



Physical examination on admission revealed an unusually tall, well developed but undernourished, slightly dyspneic young man, propped up in bed. At the apex a thrill was palpable, and the impulse was diffuse in the sixth interspace 15 cm. to the left of the midsternal line. The sounds were absolutely irregular, the apical rate being 80. The first sound was markedly accentuated. In the mitral area a blowing systolic murmur and a rough diastolic murmur were heard. A diastolic murmur heard at the aortic area was transmitted downward along the left border of the sternum. Râles were heard at the bases of both lungs. The blood pressure was 120 systolic and 80 diastolic. The liver was not palpable. There was no edema.

Examination of the urine and blood gave normal results. A roentgenogram of the chest taken at a distance of 7 feet showed a transverse cardiac diameter of 20 cm. and an internal diameter of the chest of 32 cm. The heart was tremendously enlarged in all directions. Electrocardiographic tracings showed auricular fibrillation, a ventricular rate of 70, a diphasic T wave in lead I and slight right axis deviation. The venous pressure was 10 cm. of water. The vital capacity of the lungs ranged from 2,900 to 3,100 cc. The velocity of blood flow (arm to tongue time) varied from forty-two to forty-five seconds. The basal metabolic rate varied from minus 1 to minus 5 per cent.

On March 25, total ablation of the normal thyroid gland was performed with the patient under gas-oxygen anesthesia; the operation required two hours and nineteen minutes. The patient did well throughout. The blood pressure rose gradually from 110 to 140 systolic. The apex rate did not rise above 105, and the respiratory rate remained at 25 per minute during the operation. The temperature rose to 100 F. on the second postoperative day and reached normal on the fifth postoperative day. The pulse and respiration showed very little elevation.

On the second day after operation the patient volunteered that the constant pressure pain in the region of the heart which had been practically continuous for twelve years had disappeared. One week later he stated that his breathing was distinctly easier, that he could breathe more normally and that the pounding of his heart which always had been present with every change in position had disappeared. He appeared alert and happy. On the tenth day he was up and about for several hours, and his only complaint was that he was not permitted more activity. On the eleventh day he contracted a slight infection of the upper respiratory tract, and this was followed shortly by one of the atypical epileptiform seizures. On the twenty-second day after operation he stated that he felt clearer mentally than he had before operation. He again noted that his breathing was considerably better and that he could walk up and down the corridor without any appreciable shortness of breath or fatigue. Critical objective study appeared to corroborate his statements.

On April 19, twenty-five days after operation, he suddenly experienced pain in the chest; examination disclosed râles confined to the base of the left lung. Respiratory distress with profuse perspiration followed, and he coughed up large amounts of blood-tinged frothy sputum. A roentgenogram of the chest showed a definitely increased density over the left lung, somewhat more marked in the region of the upper lobe. The history of similar attacks in the past, the knowledge that he had fibrillation, the character of the onset and the physical findings strongly suggested the occurrence of pulmonary infarction.

Recovery from this attack was complete, but in the course of the next two weeks two other short attacks characterized by sudden dyspnea and the coughing up of pinkish froth occurred. These attacks lasted only a few minutes, and there was no recurrence. The patient continued to show the same improvement



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*Comment.*—This patient, a man 22 years of age, with rheumatic heart disease, mitral stenosis and extreme cardiac enlargement gave a history of numerous attacks of congestive failure during the course of the past twelve years. He had attacks of massive hemoptysis suggestive of pulmonary infarction, and shortly before admission hematuria consistent with renal infarction. Ever since he could remember he had been conscious of pain in the region of the heart. After operation he showed significant improvement. Pain in the chest, palpitation and orthopnea disappeared. His response to exercise was attended with considerably less shortness of breath than was manifest in the tests before operation. At the time of writing, four months after operation, the basal metabolic rate remained persistently lowered, the velocity of blood flow was correspondingly prolonged, and the patient continued to show clinical improvement.

CASE 3.—*Syphilis, arteriosclerotic heart disease and congestive failure for six years.*

C. C., a man, aged 66, entered the Beth Israel Hospital on March 16, 1933. The family and past histories were irrelevant. He lived an active and vigorous life until the onset of his present illness.

In November, 1926, about six and a half years before entry, he contracted a cold in the head and a nonproductive cough which, while not very severe, failed to respond to treatment. At about the same time he was troubled by a feeling of "tightness in the chest" particularly at night, and noted the onset of shortness of breath, violent palpitation and marked weakness on slight exertion. His legs became swollen, and he was forced to stop work. After the administration of digitalis and rest in bed his condition improved. On returning to work six years before admission, the foregoing signs and symptoms recurred. During the next four years he was forced to spend much of his time in bed. His discomfort gradually increased; he became dyspneic while at rest and had to sleep propped up in bed. About two years before admission (February, 1931) he fainted on the street and was taken to the Boston City Hospital, where he remained for five weeks. Because of complete incapacitation he was transferred to a hospital for chronic diseases, where he remained until admission to the Beth Israel Hospital.

During the two years' stay at the State Infirmiry he had repeated attacks of dyspnea, orthopnea, cyanosis, edema of the legs, loss of appetite and slight elevation of temperature, which came on about once every two months and lasted for a week. Between attacks he was quite comfortable, provided he remained in bed or in a chair.

Physical examination showed a well developed and moderately well nourished man. The retinal and peripheral vessels showed advanced arteriosclerosis. The apex impulse was seen and felt in the sixth interspace in the anterior axillary line. There were no thrills. The rhythm was regular except for many premature beats. A loud systolic murmur and a short diastolic murmur were heard in the mitral area, and a systolic murmur in the aortic area. The lungs were clear. There was no hepatic enlargement or peripheral edema. The blood pressure ranged from 130 systolic and 60 diastolic to 110 systolic and 70 diastolic. The vital capacity of the lungs varied from 2,700 to 3,300 cc. The weight was 134 pounds (60.8 Kg.).



change in the height of the T waves or in the voltage of the QRS complexes. Exercise tolerance tests showed a definite improvement compared to the response before operation in that dyspnea was less and the pulse and blood pressure returned to normal in a shorter time. Slight pallor and definite anemia developed after operation, the red count being 5,000,000 before operation and dropping to 4,180,000 and 3,890,000 on the nineteenth and thirty-second days after operation. Chart 3 shows the changes in the basal metabolic rate and the velocity of blood flow. The basal metabolic rate dropped rapidly, reaching minus 37 per cent on the thirty-third day after operation. The velocity of blood flow, which had been retarded as a consequence of cardiac insufficiency, became more prolonged as an adjustment to the diminished basal metabolic rate.

About the thirty-third day after operation the patient became increasingly drowsy, weak, apathetic and slow mentally. His skin was dry, and his appetite became poor. The vital capacity fell to the preoperative level. The blood cholesterol increased from its previous level of from 154 to 147 to 207 mg. per hundred cubic centimeters. Electrocardiographic tracings and roentgen measurement of the heart showed no significant changes. Râles appeared at the bases of both lungs, but there were no signs of peripheral edema. The patient had insomnia since the onset of his illness and had been receiving daily doses of barbital. The sudden onset of drowsiness was therefore considered as probably due to barbital poisoning, but since the basal metabolism had fallen to minus 37 per cent, myxedema as a cause could not be ruled out. Therefore, all sedatives were omitted, and 3 grains (0.195 Gm.) of thyroid extract was given daily for seven days. The basal metabolic rate rose to minus 13 per cent, and the velocity of blood flow increased strikingly. Premature auricular beats reappeared. The patient regained his former alertness and vitality, slept soundly at night and after a short rest in bed was able to walk without dyspnea or any evidence of congestive failure. He stated that he had not felt so well at any time during the preceding six years.

*Comment.*—This patient, a man aged 66, with a history of congestive failure of six years' duration and laboratory evidence of syphilis, showed striking improvement following total thyroidectomy. Palpitation, orthopnea and dyspnea disappeared, and the ability to perform exercise was definitely improved. At the time of writing, four months after operation, he was able to be up and about without dyspnea or edema. The vital capacity increased 600 to 1,200 cc. above the level before operation, and clinical improvement was paralleled by a decrease in the metabolic rate and a slowing of the velocity of blood flow.

*CASE 4.*—*Paget's disease, arteriosclerotic heart disease with hypertension, angina pectoris, cardiac asthma and congestive failure for two years.*

W. B., a man, aged 55, a shoe designer, was admitted to the Beth Israel Hospital on March 16, 1933. The past history was unimportant except for a gradual change in the shape of the long bones during the previous eighteen years. The present illness began in January, 1931, with recurring attacks of bronchitis. In March, he was suddenly awakened at night by a paroxysm of dyspnea which lasted twenty minutes. On attempting to lie flat attacks recurred and he became orthopneic; he was therefore removed to a hospital where he was digitalized and kept at complete rest in bed for five weeks. On discharge orthopnea and dyspnea on exertion persisted and increased in severity, forcing him again to enter a hospital, where he remained for six weeks. He felt somewhat better but a few weeks

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portion of the amount not accounted for represented a loss due to bacterial fermentation, and he believed that the depression of the blood sugar was due to the stimulation of the insulin-producing islets by the hormone action of a small amount of absorbed dextrose. He also quoted Brugel, who found, after five hours' incubation, the disappearance of 34 per cent of dextrose subjected to fermentation in feces.

## METHOD

Patients in the ward, including both male and female and diabetic and non-diabetic persons, who had no complicating rectal disorders were used for our study. Among the nondiabetic group no patients were used in whom any metabolic

*Table Showing the Effect of the Rectal Administration of Dextrose on the Blood Sugar*

Number of Cases	Amount of Dextrose Instilled	Average Fasting Blood Sugar, Mgr.	Blood Sugar Rise Above Fasting			Per Cent Rise in Blood Sugar	Deviation in Duplicate Determination	Dextrose Recovered				Per Cent Absorbed
			Maximum	Minimum	Average			Maximum	Minimum	Average	Per Cent	
Nondiabetic												
11	250 cc. 10% (25 Gm.)	83	47	3	17	21	$\pm 2\%$	11.2	1.7	6.2	27	73
7	200 cc. 25% (50 Gm.)	83	50	2	14	17	$\pm 2\%$	14.6	4.0	9.2	18	82
5	400 cc. 5% (20 Gm.)	86	34	2	14	16	$\pm 2\%$	3.0	0.9	2.1	10	90
1	200 cc. 50% (100 Gm.)	90	..	..	22	25	$\pm 2\%$	....	...	18.3	18	82
Diabetic												
1	250 cc. 10% (25 Gm.)	312			66	21	$\pm 4\%$			9.4	38	62
1	250 cc. 10% (25 Gm.)	123			11	9	$\pm 2\%$			10.2	41	59
1	200 cc. 25% (50 Gm.)	140			4	3	$\pm 3\%$			6.0	12	88
1	200 cc. 25% (50 Gm.)	220			4	2	$\pm 3\%$	Evacuation, 1 hr.		10.7	21	79
1	400 cc. 5% (20 Gm.)	179	Decreased		35	..	$\pm 3\%$			2.7	14	86
1	400 cc. 5% (20 Gm.)	145			73	50	$\pm 3\%$			1.2	6	94
1	400 cc. 5% (20 Gm.)	237			88	38	$\pm 4\%$			2.7	14	86
1	400 cc. 5% (20 Gm.)											

disorder was found or suspected. Experiments were performed when the patient was in a fasting state in the morning, fourteen hours after a previous meal. A cleansing enema was first given, which was followed by an effective evacuation of the bowel. Blood was then drawn and citrated. One hour after the enema, dextrose was instilled into the rectum in amounts which ranged from 20 to 100 Gm. in various concentrations. The dextrose was uniformly dissolved in distilled water. It required approximately a minute to instill this solution. Specimens of blood were then drawn at intervals of thirty, sixty and one hundred and twenty minutes after the instillation. Estimations of the blood sugar were performed in duplicate by the Folin-Wu method. No results were accepted when the duplicate deviation was more than 3 per cent. The series consisted of twenty-four nondiabetic patients, eleven of whom received 250 cc. of a 10 per cent dextrose (25 Gm.); seven, 250 cc. of a 25 per cent solution (50 Gm.); five, 400 cc. of a 5 per cent solution (20 Gm.) and one, 200 cc. of a 50 per cent solution (100 Gm.). Two of the diabetic patients received 250 cc. of a 10 per cent solution of dextrose (25 Gm.); two, 200 cc. of a 25 per cent solution (50 Gm.), and three, 400 cc. of a 5 per cent solution (20 Gm.).

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# PLEURISY IN RHEUMATIC FEVER

## CLINICAL OBSERVATIONS

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AND

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Pleural involvement in rheumatic fever is an important episode in the course of the disease. Lesions may result from some complication, such as myocardial failure or pulmonary infarction, or may be due to the disease itself, as are the more common involvements of the synovia, myocardium, endocardium and pericardium. Fifteen cases of rheumatic fever in which there was undisputed evidence of pleural involvement have been studied. For purposes of discussion we have divided them into two groups: (1) thirteen cases of true rheumatic pleurisy and (2) two cases of bilateral hydrothorax accompanying myocardial failure.

### FIBRINOUS PLEURISY

CASE 1.—A girl, 15 years of age, was admitted to the hospital, complaining of a sharp pain in the left axilla, which was increased in severity on inspiration. Six years and three years previously she had had rheumatic fever. Twelve days before admission, following recovery from a mild cold in the head, she was seized by a sudden, severe, stabbing pain in the left axilla, which lasted a few hours. The pain was increased on inspiration. On the following morning she complained of general malaise and moderately severe pain and swelling of all her joints; she had a temperature of 102 F. With salicylate therapy, the pain in the joints immediately subsided and the temperature returned to normal. Five days before entering the hospital, the sharp, severe pain in the anterior left axilla recurred. It persisted, but was described at the time of admission as being dull, except on inspiration, when the pain became knifelike. There had not been cough, sputum or hemoptysis.

Tonsillectomy and adenoidectomy had been performed immediately after the first attack of polyarthritis. The patient had rarely had sore throat. Her general health had been good, except for the recurrent attacks of rheumatic fever.

At the time of admission to the hospital, the temperature was 104.4 F.; the pulse rate was 100, and respirations were 24 per minute. The patient was well developed and fairly well nourished. A small amount of tonsillar tissue was noted on the left side of the throat, and the pharynx was slightly injected. The sub-maxillary lymph nodes were slightly enlarged but were not tender. Respiratory excursions of the chest were limited. In the left axilla the percussion note was dull; the voice and breath sounds were only faintly heard and tactile fremitus was

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital; and the Department of Medicine, Harvard University Medical School.



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hospital for several months because of rheumatic fever. His symptoms had been relieved by salicylates. He had been told that he had "heart trouble." Tonsillitis had been infrequent. One month before admission, he had a severe sore throat, which subsided promptly, but recurred slightly several times during the intervening month. Two weeks later, his ankles became painful and swollen, but the pain and swelling had subsided within twenty-four hours, so that he was able to return to work. Nine days before admission, the ankles became so painful and swollen that he was confined to bed. His temperature was elevated and many joints were swollen. For six days he was dyspneic and orthopneic and had a disturbing paroxysmal cough productive of small amounts of tenacious material. He had had several mild epistaxes.

At the time of entry, the temperature was 103 F., the pulse rate, was 102 per minute, and the respiratory rate was 28. The patient was well nourished, moderately well developed, slightly dyspneic and orthopneic. The facial expression was one of anxiety. The skin was warm and moist. There was a slight cyanosis of the lips and nail beds. The tonsils were red and inflamed. The respiratory excursions were symmetrical but shallow. Examination of the left lung revealed a few coarse, crackling râles at the base posteriorly. The percussion note over the right base posteriorly and below the right clavicle anteriorly was impaired. Tactile fremitus and voice sounds were increased, and bronchovesicular breath sounds occurred over these areas. On percussion the heart was found to be slightly enlarged. The outline was that of a mitral deformity. The first sound, at the apex, was snapping; the pulmonic second sound was accentuated; a blowing systolic murmur was heard over the apical region and a short, high-pitched, mid-diastolic murmur was heard inside the apex. The systolic blood pressure was 90; the diastolic, 60. The edge of the liver was palpable on deep inspiration. The elbows, knees and ankles were swollen, tender and slightly painful on motion.

On the day after entry, the roentgenologic study showed patchy density throughout both lungs, which was more marked in the right lung. On the following day, a pericardial friction rub was heard over the base of the heart, which was later audible over the whole precordium. The pericardial friction rub persisted for two and a half months. The signs over the lungs remained the same for ten days, when a pleural friction rub and bronchial breath sounds were heard in the left axilla and signs of a considerable amount of fluid appeared gradually at the right base. Seven hundred and seventy-five cubic centimeters of pinkish yellow fluid was removed from the right side of the chest. Clot formation was noted within ten minutes. There were 4,100 red blood cells per cubic millimeter, and 1,250 leukocytes, of which 32 per cent were polymorphonuclears and 68 per cent were lymphocytes. The fluid on bacteriologic culture remained sterile. The signs of patchy consolidation at the base of the right lung persisted for a week. There was clinical and roentgenologic evidence of a small amount of fluid at the bases of both lungs for another week. The temperature remained elevated for a month after the patient's admission, returning to normal gradually a week after pleurocentesis.

In spite of the administration of 100 grains (6.4 Gm.) of sodium salicylate, the joint symptoms were not entirely relieved while there was clinical evidence of pulmonary and pericardial lesions. There was no demonstrable effect of the salicylate therapy on the pulmonary and pericardial lesions. The pulse rate remained elevated for three months. Respirations remained between 28 and 36 per minute throughout the four weeks during which there were obvious pleural and pulmonary lesions. Convalescence was uneventful. Seventeen weeks later, at the time of the patient's discharge, the lungs and pleura showed no evidence of lesions, either clinically or roentgenologically. The heart at this time showed a

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recurrences of polyarthritis and one attack of Sydenham's chorea. The development of the signs of a mitral disease were observed. During the three years preceding his fifth and last admission he had been free from symptoms; he had continued in school and had played baseball, football and hockey. Ten days prior to the last entry, a severe sore throat developed, which was followed by pain, tenderness, redness and swelling of the ankles, knees and left wrist. During the week before admission he had a temperature as high as 102 F.; on several occasions he was nauseated and vomited; there was an intermittent dull aching over the precordium, and he had one profuse epistaxis.

At entry, the temperature was 100.4 F., and the pulse and respiratory rates were 80 and 24 respectively. The patient was well developed and well nourished, with a pale, hot, moist skin. The lips were cyanotic. The pharynx was injected. There were forceful pulsations of the vessels of the neck. The heart was enlarged and systolic and diastolic murmurs were heard over the base and the apex. There were peripheral signs of aortic regurgitation. Respiratory movements were rapid. Below the angle of the left scapula were dullness, increased whispered and voice sounds and a few medium moist râles. The right elbow, wrists, ankles and knees were red, hot, swollen and tender; the left shoulder was painful on motion.

On the day following admission, a pericardial friction rub was heard, which persisted during the two following days. The heart sounds were faintly heard and the pulse became of poor quality. The temperature reached 103 F.; the pulse rate increased to 140, and the respiratory rate mounted to 60. Sodium salicylate was given in doses of 150 grains (9.7 Gm.) daily, with no effect other than relief from the pain in the joints. Peripheral edema appeared and signs of pulmonary congestion, with the collection of rather large amounts of fluid at both bases of the lungs, were observed. The course was rapidly progressive, and death occurred five days after admission.

The roentgenogram of the chest, taken the day after entry, showed cloudy pulmonary fields (stasis). The total width of the heart shadow was 17.8 cm.; the inner diameter of the chest was 28 cm. The electrocardiogram, taken the same day, showed sino-auricular tachycardia, a pulse rate of 107, a PR interval of 0.2, T<sub>2</sub> diphasic and T<sub>3</sub> inverted. The blood, at the time of admission showed 16,500 leukocytes per cubic millimeter, 3,460,000 erythrocytes and 65 per cent hemoglobin. The differential leukocyte count revealed 82 per cent polymorphonuclears, 9 per cent lymphocytes and 9 per cent monocytes. A blood culture taken the day before death was sterile.

At autopsy, the right pleural cavity contained 500 cc., and the left, 200 cc., of thin yellow fluid. The pleural surfaces were smooth and glistening and were free from deposits of fibrin; no flecks of fibrin were found in the fluid. The lungs showed chronic passive congestion. The pericardial cavity was almost completely obliterated by fairly firm fibrous adhesions. Some fresh fibrin was deposited over the right auricle. The heart was markedly hypertrophied, weighing 760 gm. The myocardium showed atrophy of the muscular fibers. The cusps and leaflets of the mitral and aortic valves were opaque and slightly thickened; there was a single line of small, friable, yellowish-red vegetation along the free borders of these valves. The chordae tendineae were thickened and shortened. The lining of the endocardium of the right side of the heart was normal; the aorta was smooth and elastic.

The patient, with a rheumatic history of over ten years' duration, on admission to the hospital, showed polyarthritis, endocarditis, pericarditis

## DIAGNOSIS OF GONOCOCCUS ENDOCARDITIS

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Cases of gonococcus endocarditis have been reported not infrequently in the literature. Up to 1912, according to McCants, there were a hundred cases published. Since 1912 we have been able to collect forty-eight cases. Table 1 summarizes the evidence on which the diagnosis of these cases was made. The two cases which had the most complete diagnostic evidence were those of Grenet, Laurent, de Pfeffel and Levent, and of Riecker. In these cases the blood culture, bacteriologic morphology, cultural characteristics, fermentation and agglutination reactions were all positive. Huebschmann's case had a positive history, blood culture, postmortem culture, bacteriologic morphology and cultural characteristics. There were four cases that had a positive history, blood culture, bacteriologic morphology and cultural characteristics (Thayer, case 11, Laserre, Dwyer, Kramer and Smith). Two cases (Vander Veer and Kirkland) had a positive history, postmortem culture, bacteriologic morphology and cultural characteristics, but a negative blood culture. Nine cases had positive blood cultures and two other positive findings. Two cases had positive blood cultures and one other positive finding. Five cases did not have positive blood cultures, but did have three other positive findings. Ten cases did not have positive blood cultures, but did have two other positive findings. Thirteen cases had nothing on which to base the diagnosis of gonococcus endocarditis except the presence of clinical endocarditis and the history of gonorrhea.

In the case that we were recently able to study carefully, the diagnosis of acute endocarditis was evident clinically and was demonstrated at autopsy. Bacteriologically, the organism grown from the blood stream and from the vegetation on the aortic valve post mortem was identified as a gonococcus by its morphologic and cultural characteristics, fermentation reactions, agglutination, precipitin and complement fixation

TABLE 1.—Evidence for Diagnosis of *Gonococcus Endocarditis* in Patients with Clinical Signs of *Endocarditis*

Author	History of Gonorrhea	Blood Culture	Post-mortem Culture	Bacteriologic Morphology	Cultural Characteristics	Fermmentation Reactions	Agglutination	Precipitation	Complement Fixation	Comments
Thayer: Case 1.....	..	—	+	+	..	..	..	..	.....	Prostatic fluid showed gram-negative diplococci
Case 2.....	..	—	..	+	..	..	..	..	.....	Necropsy performed 5 days after death
Case 3.....	..	—	+	+	..	..	..	..	.....	
Case 4.....	..	+	..	+	+	..	..	..	.....	
Case 5.....	+	+	..	+	..	..	..	..	.....	
Case 6.....	+	—	—	+	..	..	..	..	.....	
Case 7.....	+	+	..	+	..	..	..	..	.....	Postmortem smear, but no culture
Case 8.....	..	+	..	+	..	..	..	..	.....	Postmortem smear, but no culture
Case 9.....	..	+	..	+	..	..	..	..	.....	Postmortem smear, but no culture
Case 10.....	+	—	..	..	..	..	..	..	.....	No bacteriologic examination at necropsy
Case 11.....	+	+	..	+	+	..	..	..	.....	No bacteriologic examination at necropsy
Case 12.....	+	—	..	..	..	..	..	..	.....	No bacteriologic examination at necropsy
Case 13.....	+	—	..	..	..	..	..	..	.....	
Navarro, Pueyrredón and Elizalde.....	+	—	..	+	..	..	..	..	.....	Pus smeared; no bacteriologic examination post mortem
Laserre .....	+	+	..	+	+	..	..	..	.....	
Berner .....	+	—	..	+	..	..	..	..	.....	Postmortem smear, but no culture
Thayer and Blumer.....	..	+	..	+	+	..	..	..	.....	Postmortem smear, but no culture
Vander Veer .....	+	—	+	+	+	..	..	..	.....	
Hubschmann .....	+	+	+	+	+	..	..	..	.....	
Küls .....	+	..	+	+	..	..	..	..	.....	
Dwyer .....	+	+	..	+	+	..	..	..	.....	No postmortem bacteriology
Johnston and Johnston.....	+	—	..	+	..	..	..	..	.....	Postmortem smear, but no culture

Lindau .....	+	-	+	+	..	..	..	..
Buquet and Jaureguy.....	+	..	..	+	..	..	..	..
Edwards .....	+	-	..	+	..	..	..	Postmortem smear, but no culture
Aubertin and Gambillard.....	+	-	..	..	..	..	..	Recovery after antigenococcus serum
Haase: Case 1.....	+	..	..	+	..	..	..	Smear but no culture post mortem
Case 2.....	+	-	-	+	..	..	..	..
Schaeffer and Baron.....	+	..	..	..	..	..	..	'Spinal fluid culture negative; recovery
Proschaska (3 cases).....	+	+	..	+	..	..	..	..
Kramer and Smith (3 cases...).....	+	2 = -, 1 = +	..	+	..	..	..	..
Charvet and Lesieur.....	+	..	?	..	..	..	..	Postmortem cultures showed streptococcus; gonococcus from urethra
Mouisset and Chaliar.....	+	..	..	..	..	..	..	..
Klein .....	+	-	..	..	..	..	..	..
Bard, Langeron and Gardère.....	+	..	..	..	..	..	..	..
Lupu and Stoënescu.....	+	-	..	..	..	..	..	No bacteriology post mortem
McCants: Case 1.....	..	-	..	+	..	..	..	..
Case 2.....	..	..	..	+	..	..	..	Smear obtained post mortem, but no culture
Grenet, Laurent, de Pfeffel and Levent	+	+	..	+	+	+	..	Agglutination with antimeningococcus was negative; smear obtained post mortem positive
Riecker .....	..	+	-	+	+	+	..	..
Kirkland .....	+	-	+	+	..	..	..	..
Perry .....	+	+	..	+	..	..	..	Patient recovered
Gertzog and Kuzmin.....	+	-	..	..	..	..	..	Mitral vegetation post mortem; post-mortem smear
Hoffman and Taggart.....	..	+	..	+	..	..	..	Postmortem smear showed gram-negative intracellular diplococci; no culture post mortem
Case herein reported.....	..	+	+	+	+	+	+	Organism against anti-gonococcus smear +

reactions. As meningococcus endocarditis may occur without meningitis (Bancker and Lorentz), we believe that the aforementioned procedures are of value in the positive identification of the gonococcus in a case of endocarditis.

#### REPORT OF A CASE

*Clinical History.*—G. W., a Negress, aged 20, was admitted to the maternity ward of the Boston City Hospital on Jan. 29, 1931. The past history was essentially irrelevant. She had had two previous normal pregnancies. There was no history of tonsillitis, chorea, rheumatic fever, shortness of breath, edema, palpitation or precordial pain. The date of the last menstruation was May 1, 1930. She had been followed in the prenatal clinic, where her pregnancy proceeded uneventfully. It was noted that the patient had a systolic murmur at the mitral area. There were no toxic symptoms, and no bleeding. The baby was active. The patient was admitted to the hospital with labor pains of five hours' duration. She gave a history of a cold in the head for the past ten days. The temperature on entry was 101 F., and the pulse rate, 90 per minute. Obstetric examination showed signs of a full-term pregnant uterus.

*Examination.*—The day following admission the patient delivered a normal baby without anesthesia. The delivery was natural in every way. The placenta and membranes were intact. Physical examination at this time revealed nothing abnormal. There were no heart murmurs. On the third day post partum, the temperature was again 101 F., the pulse rate, 120, and the respiratory rate, 24. At this time, a productive cough developed, and the patient raised thick grayish mucoid material. No blood was noticed. A medical consultant at this time reported a few crepitant râles at the right base posteriorly and extending up into the right axilla. There were no signs of frank consolidation, and the opinion was expressed that the patient probably had an acute upper respiratory infection with some bronchopneumonia. At this time the patient was eating well and sleeping well. She was digitalized and then put on a maintenance dose of digitalis daily. On February 4, a systolic murmur reappeared in the mitral area and remained localized there. On February 6, the patient coughed up frank bloody sputum. During the next two days, she raised about 3 ounces (89 cc.). On February 8, the bloody character of the sputum subsided. The patient had no complaints except for cough. About 11:30 a. m. on February 10, twelve days after entry, the patient had a severe chill which lasted about fifteen minutes. When seen immediately afterward, she had complete right hemiplegia involving the leg, arm, palate, tongue, face and eyes. There was paralysis of lateral gaze to the right. The patient did not respond to questioning, although she appeared conscious and seemed mentally alert. She appeared to have a complete aphasia. Reflexes were present, but were diminished in the right arm and absent in the right leg, with a suggestively positive Babinski sign on that side. There was no stiff neck or Kernig sign, and the pupils reacted normally. A pelvic examination revealed no abnormality. The blood pressure was normal. Examination of the heart showed no enlargement to percussion. The sounds were regular and of good quality. A long systolic murmur was audible throughout the precordium, and a questionable diastolic murmur was present in the aortic area. The patient was transferred to the neurologic service for study.

A complete examination at this time revealed, in addition to the foregoing findings, the following: The patient was a well developed and nourished young Negress. The throat was injected; the tongue was coated, and the skin was warm and moist. There was diminished expansion of the right side of the chest, with diminished tactile fremitus and diminished resonance on that side. Crepitant râles were heard over the base of the left lung. The systolic murmur was present



throughout the precordium, but was loudest in the aortic area. A diastolic murmur was also heard in the aortic area, transmitted to the neck. No petechial spots could be found. There were a complete right hemiplegia and a complete motor aphasia, with a large sensory element. The patient could apparently understand spoken language only slightly. She could not carry out simple commands, although she seemed to understand the meaning of gestures and facial expressions. The abdominal reflexes were absent. There was a definite Babinski sign on the right.

*Laboratory Work.*—The Kahn and Wassermann reactions of the blood were negative. On February 3, the white blood count was 15,000 per cubic millimeter; on February 5, a blood culture was negative. On February 9, the white count was 16,000 per cubic millimeter; examination of the sputum showed it to be non-foul; it contained no gross blood, free particles or acid-fast organisms, gram-positive diplococci were predominant; no Vincent's organisms were seen.

On the neurologic service, lumbar punctures showed the results given in table 2.

In all the lumbar punctures, the dynamics were normal. In each tap, the first fluid removed seemed to have more blood in it than the last. After centrifugation there was xanthochromia in the supernatant fluid. The nonprotein nitrogen in a specimen taken on February 11 was 24 mg. Smears showed no organisms. On

TABLE 2.—Results of Lumbar Puncture

Date	Initial Pressure, Mm. of Water	Color	Clot	White Blood Cells per Cu. Mm.	Red Blood Cells per Cu. Mm.	Pandy Test	Total Protein, Mg.	Sugar, Mg.	Culture
2/10	90	Blood-tinged	0	4,000	5,000	+	153	74	No growth
2/11	80	Blood-tinged	0	3,500	16,250	+	174		
2/12	100	Blood-tinged	0	500	4,000	+	51	120	
2/13	110	Blood-tinged	0	120	4,500	+	..	85	No growth

February 10, the chloride was 729 mg., and on February 11, 650 mg. (expressed as sodium chloride). On February 10, the Wassermann reaction was negative. On February 11, the urine was negative. The hemoglobin was 75 per cent (Tallqvist); the red blood cells numbered 3,380,000; the white blood cells, 15,950. A differential count showed: 82 neutrophils, 16 lymphocytes, 1 eosinophil and 1 large monocyte. There was a very slight change in the size and shape of the red blood cells. Platelets were abundant. The Kahn reaction of the blood was negative. A blood culture showed a gram-negative diplococcus. A roentgenogram of the chest showed a slight density at the base of the right lung, probably resolving pneumonia. Otherwise, the lung fields were clear. A cervical smear showed gram-negative diplococci, some intracellular. On February 12, the blood sugar was 108 mg. per hundred cubic centimeters. On February 17, the red blood cells numbered 5,401,000; the white blood cells, 26,850. A differential count showed: 82 neutrophils, 13 lymphocytes, 1 basophil and 4 large monocytes. An electrocardiogram revealed: sinoauricular tachycardia; rate, 125; P R interval, 0.14 second; Q R S 0.08 second; T<sub>1</sub>, low; T<sub>2</sub> and T<sub>3</sub>, diphasic; axis, normal. There was a high skin resistance.

*Course.*—The temperature, which was 102 F. on entry to the neurologic service, varied from normal to 104 F.; it averaged about 101 F. The pulse rate maintained a fairly constant level at 120. It occasionally went as low as 100 and as high as 140. The respiratory rate was usually about 45. It was as low as 30 and often as high as 50. During the first few days in the ward, the patient seemed to show considerable improvement. She became more alert, but her aphasia con-

tinued. The hemiplegic side remained largely flaccid for the first two days and then began to become spastic. No return of function took place. The gram-negative diplococcus which was grown from the blood stream was found to agglutinate with both antimeningococcus and antigenococcus serums. Sugar fermentation tests were carried out, but owing to technical difficulties a report was not received for some time. However, it was thought advisable to give the patient antimeningococcus serum, since the organism in her blood was agglutinated by the serum in spite of the fact that it probably was a gonococcus.

The patient's respiratory difficulty began to increase, and the signs of bronchopneumonia seemed to be spreading to the left side as well as to the right. On February 18, the patient was given antimeningococcus serum, after a skin test was performed and found to be negative. Only 7 cc. could be introduced into the vein; 30 cc. was given intramuscularly. At the time of the injection, the patient's

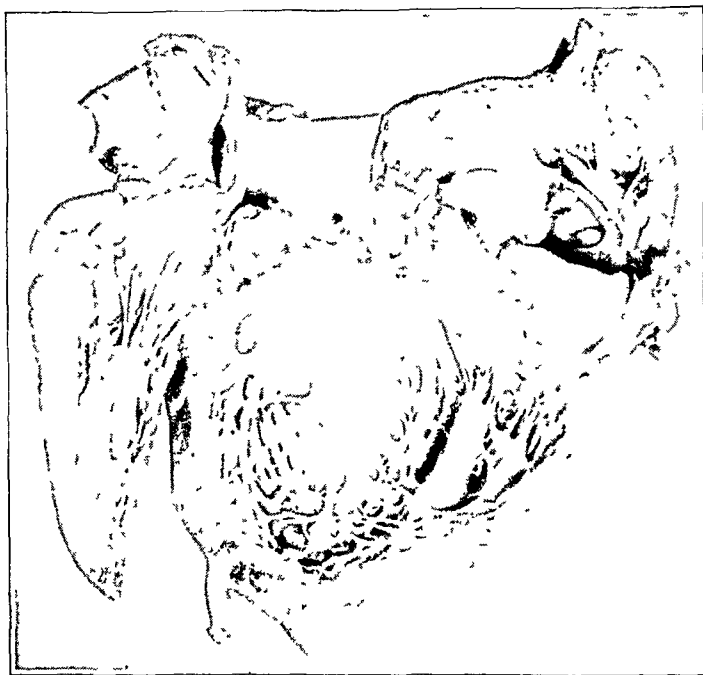


Fig. 1.—Vegetation on the anterior cusp of the aortic valve.

respiratory difficulty was becoming extreme. Half an hour later acute pulmonary edema developed. Her lungs rapidly filled; her respirations became extremely labored, and blood-streaked froth appeared at her mouth. Epinephrine, atropine and morphine were given without any improvement. The patient became rapidly worse and died about an hour after the serum was given. Artificial respiration was of no avail.

*Clinical Diagnosis.*—The diagnosis was gonococcal sepsis; endocervicitis; endocarditis with involvement of the aortic valve; embolus to the left internal capsule of the brain; resolving pneumonia of the lower lobe of the right lung; acute terminal pulmonary edema.

*Necropsy Report.*—Necropsy was performed on February 18, eighteen hours post mortem.

*External Description:* There exuded from the mouth a thin, brownish fluid. The abdomen was slightly distended.

Two hundred cubic centimeters of straw-colored fluid was found in the peritoneal cavity, chiefly in the pelvic portion. The stomach showed marked distention

and extended to within 2 cm. of the umbilicus. The edge of the liver was 8 cm. below the xiphoid and 3 cm. below the right costal border in the midclavicular line.

Both pleural cavities contained about 300 cc. of straw-colored fluid. There were fine fibrous adhesions throughout both cavities.

The heart weighed 320 Gm. It was normal in size. The epicardium was smooth and glistening. The myocardium was pale red and flabby; there was no gross evidence of fibrosis. On the anterior cusp of the aortic valve was found a soft, friable, grayish-yellow, rounded vegetation 1.6 cm. in diameter, partially obstructing the opening of the right coronary artery. The right and left posterior cusps of this same valve were smooth and of normal thickness. The other valves and the endocardium were normal. The coronary arteries were normal.

In both lungs there was diminution in crepitus, with a large area of consolidation in the lower lobe on either side. Section through the consolidated portions showed a grayish cut surface from which pus exuded on pressure. The cut surface of the remaining pulmonary tissue was grayish red and moist. Over the mucosa of both bronchi there was exudate.

The spleen weighed 390 Gm., and it was several times the normal size. The organ was soft, and the capsule was moderately tense. The surface showed numerous pale yellow, poorly demarcated areas of infarction varying from 1 to 4 mm. in diameter. The cut surface of the uninfarcted areas was purplish red. The pulp was extremely soft in consistence.

The stomach was dilated. When it was opened, it was found to contain from 300 to 400 cc. of light greenish fluid; the mucosa was normal.

The pancreas was normal.

The liver weighed 1,640 Gm. and was normal in size. The surface was smooth and yellowish red. The consistence was firm. Multiple sections revealed no gross pathologic changes other than congestive mottling. The gallbladder and bile ducts were normal.

The kidneys weighed 260 Gm. Both organs were slightly smaller than normal. Externally, they were grayish red. On section, the parenchyma showed prominent dark red pyramids and a well demarcated grayish-red cortex slightly thicker than normal. The capsule stripped easily and left a smooth external surface. The pelves and ureters were normal.

The suprarenal glands were normal.

The bladder was contracted. The mucosa was thickened and grayish red. Over the surface there was a greenish, creamy exudate. The urethra was opened from the external orifice inward and was found to be mildly injected and to contain a thin exudate.

The cervix showed mild lacerations. It measured 2 cm. across. The mucosa of the endocervix was dark red and was covered with a sanguineous, mucoid exudate. The endometrium was thickened and dark red. The uterus was slightly larger than normal, but otherwise was normal. The tubes were essentially normal in size. On the right, the fimbriated end of the tube was attached by delicate adhesions to the surface of the ovary.

The aorta was normal.

The brain weighed 1,310 Gm. There was much edema and congestion, and the meninges were opalescent. Section showed an area of softening on the left, extending the entire length of the external capsule and involving the external capsule and the putamen. This area was yellowish brown and necrotic, and was about 2 cm. in diameter. It did not extend to the surface or into the ventricle.

Anatomic Diagnoses: These were: acute vegetative endocarditis of the aortic valve; infarcts of the spleen; encephalomalacia; cystitis; moderate chronic endocervicitis; bronchopneumonia; pleural effusion.

**Microscopic Examination:** There was edema of the heart. There was infiltration of the stroma, with a few lymphocytes and large mononuclear leukocytes.

Many of the alveoli of the lungs were distended and contained fibrin, serum and large mononuclears; a few had in addition red blood cells and a sparse number of polymorphonuclear leukocytes. Early organization was seen in a few areas. The alveolar capillaries were engorged.

Immediately beneath the capsule of the spleen there was an area of necrosis surrounded by hemorrhage. The blood sinuses were markedly distended. The pulp contained many polymorphonuclear leukocytes, plasma cells, large mononuclears and lymphocytes.

The sinusoids of the liver were distended and filled with polymorphonuclear leukocytes.

There was edema of the stroma of the pancreas.



Fig. 2.—Area of softening in the left external capsule and putamen.

The renal glomeruli were distended and congested and contained polymorphonuclear leukocytes and large mononuclears; there was slight cellular proliferation of the tufts. The tubules showed desquamation of the epithelium; the lumens were filled with desquamated material; some contained serum. There were a few small focal areas of lymphocytes.

The suprarenal glands were normal.

One area of the aorta showed an accumulation of fatty, large mononuclears immediately beneath the intima.

The ovary and the tubes were normal.

There were congestion and edema of the uterine wall. Many of the blood vessels were thrombosed.

There were lymphocytic infiltration and edema of the cervix. There was slight cystic dilatation.

Sections of the area of softening of the brain showed necrosis. There was congestion of the blood vessels, with perivascular infiltration of polymorphonuclear leukocytes, plasma cells and large mononuclears. The section with the meninges

attached showed slight infiltration of the meninges, with polymorphonuclear leukocytes, plasma cells and large mononuclears.

Microscopic Diagnoses (in addition to the gross diagnoses): These were: bronchopneumonia with a small amount of organization; mild acute intracapillary glomerulonephritis; no evidence of salpingitis.

*Bacteriology.*—From the antemortem blood cultures a gram-negative, biscuit-shaped diplococcus was obtained. This organism was successfully cultured and passed to dextrose and maltose, from which a fermentation reaction characteristic of gonococci was obtained. At the time of autopsy, smears were taken from the heart valve, urethra, endocervix, fallopian tubes and the area of encephalomalacia. An organism identical in morphology to that obtained from the antemortem blood cultures was obtained from the heart valve and endocervix. The urethra showed a gram-negative diplococcus which was in every case extracellular, scattered among a wide variety of contaminating organisms. The smear from the endocervix showed a fair number of intracellular, gram-negative diplococci scattered among the usual saprophytic flora.

Cultures were made from all of the aforementioned regions; in addition, the blood from the heart was cultured. Pure cultures were obtained from the aortic valve and from the blood. The culture from the endocervix showed an overgrowth of contaminating flora. Smears made from this culture showed a gram-negative, biscuit-shaped diplococcus, but culturally its isolation was not accomplished, and no conclusion could definitely be made as to its identity. The cultures from the brain and fallopian tubes were not productive of growth. The following information is with reference to the organism obtained from the vegetation and from the blood from the heart.

*Morphology and Cultural Characteristics:* The organism was a gram-negative diplococcus, varying in size and in intensity of staining reaction, dilute carbol fuchsin being used as a counterstain in Gram's method.

Growth was readily obtained on sheep's blood beef infusion agar and ascitic fluid agar. The organism would grow but scantily on Loeffler's serum medium or in blood serum broth. No growth took place in beef infusion broth or on plain agar.

Twenty hours' incubation gave growth, but the best cultural definition came at the end of forty-eight hours. The colonies were small, discrete, round, colorless, moist, glistening, elevated, nonhemolytic and nonpigment producing.

*Fermentation Reactions:* Conclusive reactions were obtained in forty-eight hours with hormone broth with 1 per cent dextrose and 1 per cent maltose enriched with ascitic fluid. Reactions were complete at seventy-two hours. Control tubes were inoculated with known cultures of meningococci and gonococci. Uninoculated tubes corresponding to the foregoing and containing phenol red as an indicator were also incubated to preclude the possibility of contamination. At the end of twenty-four hours no change was observed in the tube containing the unknown organism, but in forty-eight hours its reaction was the same as that for the known gonococcus, attacking only the dextrose (table 3).

*Agglutination Reactions.*<sup>1</sup>—Agglutination Reactions with Polyvalent Antigoniccic Serum: Faintly turbid suspensions of twenty-four hour ascitic fluid agar

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1. All serums used in these experiments—the polyvalent antimeningococcic, the normal horse serum and the four known types of meningococci—were obtained from the Commonwealth of Massachusetts Antitoxin and Vaccine Laboratory. The types of meningococci were: type I, no. 123; type II, no. 55; type III, no. 57; type IV, no. 60 (United States Hygienic Laboratory).

cultures of the unknown organism, of a known gonococcus grown on ascitic fluid agar and of four types of meningococci grown on ascitic fluid agar were made in salt solution and kept at 56 C. for one hour. One half of a cubic centimeter of the bacterial suspensions was added to 0.5 cc. of graded dilutions of standard polyvalent antigenococcic serum. For controls, tubes of normal horse serum and bacterial suspensions and tubes of saline and bacterial suspensions were used. The tubes were kept at 55 C. for twenty-four hours, at the end of which time readings were made.

The unknown organism was identical in its agglutination reactions with the known gonococcus, the latter showing complete agglutinations from 1:200 to 1:800 and partial up to 1:1,600. Only in a dilution of 1:200 was even partial agglutination observed with three of the types of meningococci. Type IV showed no agglutination at all (table 4).

TABLE 3.—*Fermentation Reactions*

Organism	Dextrose	Maltose
Known meningococcus type I.....	+	+
Known gonococcus.....	+	—
Unknown.....	+	—
Tube uninoculated.....	—	—

TABLE 4.—*Agglutination Reactions with Antigonococcic Serum*

Strain	Final Dilutions of Antigonococcic Serum					Saline	Normal Horse Serum	Partial Agglutination	Complete Agglutination
	1:200	1:400	1:800	1:1,600	1:3,200				
Unknown organism.....	4	4	4	2	0	0	0	1:1,600	1:800
Known gonococcus.....	4*	4	4	2	0	0	0	1:1,600	1:800
Meningococcus type I....	1	0	0	0	0	0	0	1:200	0
Meningococcus type II...	1	0	0	0	0	0	0	1:200	0
Meningococcus type III..	2	0	0	0	0	0	0	1:200	0
Meningococcus type IV..	0	0	0	0	0	0	0	0	0

\* Degree of agglutination reaction: 4 = complete.

Agglutination Reactions with Polyvalent Antimeningococcic Serum: Employing the same technic, polyvalent antimeningococcic serum was substituted for polyvalent antigenococcic serum. In this instance only a faint, partial agglutination of the known gonococcus and of the unknown organism was observed and this in a dilution of 1:200. Three types of meningococci were completely agglutinated in dilutions of 1:200 and 1:400, and partially agglutinated in dilutions of 1:800 and 1:1,600. Type IV meningococcus was partially agglutinated only, and at a dilution of 1:200 and 1:400. These results are shown in table 5.

We thought that tables 4 and 5 presented definite evidence for the identification of the unknown organism as a gonococcus so far as the antigenococcic serum agglutinated (completely) the known gonococcus and the unknown organism in dilutions as high as 1:800 and agglutinated the meningococci only partially, and did this at a dilution of 1:200; also, since the antimeningococcic serum gave only a partial agglutination for the known gonococcus and the unknown organism, and did this in a dilution of 1:200. While the antimeningococcic serum partially agglutinated only the type IV meningococcus (table 4), this occurred in dilutions of 1:200 and 1:400, and this same type IV meningococcus was not agglutinated at all by the antigenococcic serum.

The following procedures were therefore carried through to supply additional evidence:

*Precipitin Reactions.*—The organism was grown for twenty-four hours on ascitic fluid agar. Each slant was washed with 3 cc. of sterile water and shaken well. The contents of the tubes were then pooled and an amount of phenol added to give a final concentration of 0.5 per cent. The material was kept at room temperature for one week and shaken daily for a period of ten minutes. The suspension was then centrifugated at high speed for one-half hour; the water-clear supernatant fluid was pipetted off and used as antigen for this test and for the complement fixation test. The precipitating serum was standard antigonococcic serum. A good precipitin ring was obtained with an antigen dilution as high as 1:800. Normal horse serum was used in place of the antigonococcic serum and saline in place of the antigen, with negative results. In the same manner, an

TABLE 5.—*Agglutination Reactions with Antimeningococcic Serum*

Strain	Final Dilutions of Antimeningococcic Serum					Normal Horse Serum	Partial Agglutination	Complete Agglutination
	1:200	1:400	1:800	1:1,600	1:3,200			
Unknown organism.....	1	0	0	0	0	0	1:200	0
Known gonococcus.....	1	0	0	0	0	0	1:200	0
Meningococcus type I....	4	4	3	1	0	0	1:1,600	1:400
Meningococcus type II...	4	4	3	1	0	0	1:1,600	1:400
Meningococcus type III..	4	4	3	1	0	0	1:1,600	1:400
Meningococcus type IV.:.	2	1	0	0	0	0	1:400	0

TABLE 6.—*Precipitin Reactions*

	Antigen Dilutions				
	1:200	1:400	1:800	1:1,600	1:3,200
Antigonococcic serum.....	4	3	2	—	—
Antimeningococcic serum.....	—	—	—	—	—
Horse serum.....	—	—	—	—	—

antigen was made from cultures of meningococci. No precipitin rings were formed (table 6).

*Complement Fixation.*—Antigen was prepared as explained. Inactivated antigonococcic serum was used as amboceptor. Two full units of complement were used throughout. Two amounts of antigen were used: 0.1 and 0.05 cc. One tenth of a cubic centimeter of antigen fixed the complement to the point where 0.002 cc. of antiserum was used. Five hundredths of a cubic centimeter of antigen fixed the complement to a point where 0.005 cc. of antiserum was used. There was no fixation when normal horse serum or antimeningococcic serum was used in place of antigonococcic serum.

#### COMMENT

The case proved of interest from three points of view: (1) obstetric, (2) neurologic and (3) medical.

1. From the obstetric point of view, it may be noted that the patient gave evidence of infection of the upper respiratory tract ten days ante

partum. Three days after delivery cough developed, which became productive of a grayish mucoid material and later frankly bloody; the temperature was 101 F. Presumably, bronchopneumonia had developed. The course of the pneumonia was rather mild, and it began to subside a week after the onset. At this time, however, the patient's pulse rate rose to 140, and the temperature continued high. Two days later chills and hemiplegia developed. It was at this time that the first definite evidence of endocarditis was found.

Wertheim, quoted by Faure-Beaulieu, demonstrated the gonococcus in the pelvic veins with or without thrombosis. It would, therefore, appear that pregnancy and parturition would predispose to extension of the bacterial invasion. Indeed, there are two other cases of gonococcus endocarditis appearing directly after parturition in the literature, Klein's and Huebschmann's. Huebschmann's case is almost identical with ours, even to the hemiplegia. Because of this relationship to parturition, the importance of antepartum treatment of gonorrhea is evident.

2. From a neurologic point of view, the case was of interest from the first as the patient showed a complete hemiplegia associated with an infection, cause unknown. The patient did not have a stiff neck or Kernig sign, but the spinal fluid was blood-tinged and had 4,000 white blood cells per cubic millimeter. Meningitis was, of course, suspected, but smears and cultures showed no organisms, and the sugar determination was normal (74 mg. per hundred cubic centimeters). At this point no serum was given because it was felt that the cells represented an aseptic meningeal reaction to an embolus close to the ventricular wall. Later when blood cultures showed a gram-negative organism agglutinated by both antimeningococcus and antigonococcus serum, antimeningococcus serum was given intravenously and intramuscularly. Although bacterial meningitis was reasonably ruled out in this case, gonococcus meningitis does occur. Lorentz reported three cases of gonococcus meningitis with good bacteriologic evidence. On the other hand, meningococcus endocarditis may occur without meningitis (Haase and Lorentz). At the time of the patient's death, the identity of the organism had not yet been fully determined.

3. From a medical standpoint, the case was interesting because of the rarity of gonococcus endocarditis. Blake, quoted by Tebbutt, is of the opinion that temporary gonococcemia undoubtedly occurs in local gonococcus infection, characterized by arthritis and synovitis. This was demonstrated in a case report by Richard C. Cabot, in which after repeated negative blood cultures a positive culture for gonococcus was obtained when the patient had a sharp rise in temperature during arthritis. The patient recovered without clinical evidence of heart disease. Bruusgaard and Thjötta reported the case of a man with purpura,



arthritis and petechiae, in which the gonococcus was cultured from the blood, purulent spinal fluid and petechiae. There was no evidence of heart disease, and this patient also recovered. Other cases of gonococcus septicemia, without cardiac involvement and with recovery, have been reported by Jenkins.

When involvement of the endocardium occurs, however, the issue is grave. Thayer reported cases in which a doubtful diagnosis was made and recovery resulted, and Perry recently reported a case (table 1) in which recovery resulted. The valve usually attacked is the aortic, although the mitral and pulmonic are sometimes involved. Complete destruction of the aortic valve has occurred (Huebschmann). Four cases of aortic aneurysms due to the gonococcus have been reported (Thayer, 1922, and Lindau).

No treatment has been of any proved value. In Perry's case, numerous transfusions were given, as well as serum from a patient who had recently recovered from gonococcus arthritis. Antigonococcus serum has been tried (O'Brien and Bancker and Aubertin and Gambillard). In our case the results of antimeningococcus serum could not be properly evaluated.

#### SUMMARY

1. Forty-eight cases of gonococcus endocarditis reported in the literature since 1912 are reviewed in tabular form with respect to the evidence on which the diagnosis was made.

2. A case of gonococcus endocarditis is reported in detail. The diagnosis of acute vegetative endocarditis was made clinically and was proved at autopsy. The organism grown from the blood stream and from the vegetation on the aortic valve post mortem was identified as a gonococcus by its morphologic and cultural characteristics, fermentation reactions, agglutination, precipitin and complement fixation reactions.

3. The case is discussed from an obstetric, neurologic and general medical point of view.

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# FACTORS CAUSING CLINICAL JAUNDICE IN HEART DISEASE

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The occurrence of jaundice in cases of heart failure was first attributed to mechanical pressure of the blood stasis in the liver. This supposition has been supplanted recently by the theory advocated by Rich and his co-workers<sup>1</sup> that jaundice in these cases is the result of anoxemia of the liver cells. The chief support for the hypothesis of anoxemia lies in the experimental observations of Binger, Brow and Branch<sup>2</sup> that pulmonary infarction is attended by anoxemia and in the numerous clinical observations<sup>3</sup> that jaundice often supervenes on pulmonary infarction. According to Rich and his co-workers, the retention of bile pigment in the blood which occurs in practically every case of outspoken passive congestion of the liver is caused by two factors, impairment of the excretory function of the liver by anoxemia and the increased burden placed on the functionally impaired liver by the demand for the excretion of a larger amount of bile pigment than normally.

While this theory adequately explains the occurrence of latent icterus in heart disease, we believe that additional factors are required to produce frank jaundice. For example, it is not clear why one patient with congestive heart failure exhibits jaundice while in another case of apparently identical or even greater severity only latent icterus develops. In order to evaluate the relative importance of the various factors involved in the pathogenesis of frank jaundice, an analysis of clinical

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and pathologic material was undertaken. The following aspects of the problem were studied:

1. The significance of pulmonary infarction in the causation of clinical jaundice both in cardiac and in noncardiac disease.
2. The relationship of the duration, the degree and the type of heart failure to the incidence of clinical jaundice.
3. The rôle played by functional and anatomic disturbances of the liver.
4. The effect of disturbed renal function.
5. The significance of quantitative factors in the formation, resorption and excretion of bilirubin as influenced by pulmonic and hepatic factors.
6. The rôle played by infection, systemic or local.

In this investigation, a series of 3,000 consecutive necropsies performed between 1926 and 1931 under the direction of Dr. Paul Klemperer were studied. From this group only those patients who died primarily of cardiac disease were selected. Cases in which the cardiac disease was merely incidental to conditions such as neoplasms, peritonitis and lobar pneumonia were not included. A total of 424 cases of primary heart disease were selected.

The association of exophthalmic goiter, diabetes mellitus and other diseases which may affect the function of the liver<sup>4</sup> was noted. In all cases, careful attention was given to the examination of the gallbladder and bile passages in order to exclude the possibility of a mechanical obstructive jaundice.

A classification of the varieties of heart disease is shown in table 1.

#### SIGNIFICANCE OF PULMONARY INFARCTION

*Incidence of Pulmonary Infarction in Heart Disease.*—Pulmonary infarction is a common complication of heart disease, particularly in congestive failure of long standing associated with mitral and tricuspid valvular disease and with auricular fibrillation. In tabulating the incidence of infarction in the various forms of heart disease (table 1), care was exercised to select only genuine infarcts. Of the 424 cases of heart disease in the series, 151, or approximately 35 per cent, were complicated by pulmonary infarction.

As is apparent from table 1 chronic rheumatic cardiovalvular disease was most frequently complicated by pulmonary infarction (almost 50 per cent), and coronary thrombosis next, with 35 per cent; bacterial endocarditis presented the lowest incidence (20 per cent).

4. Meyer, E. L.: Function of the Liver in Diabetes Mellitus, *Arch. Int. Med.* **47**:182 (Feb.) 1931. Lichtman, S. S.: Liver Function in Hyperthyroidism. *ibid.* **50**:721 (Nov.) 1932.

*Frequency of Frank Jaundice with Pulmonary Infarction.*—Frank jaundice occurred in only 17 cases, or about 4 per cent of the entire series and 10.5 per cent of the cases with pulmonary infarction. In Jolliffe's<sup>5</sup> clinical series of 231 cases of congestive heart failure, the incidence was 2.1 per cent. Of the 17 cases of frank jaundice in our series 16 were associated with hemorrhagic infarction of the lung. Eleven of these 16 patients had rheumatic cardiovalvular disease.

*Rarity of Frank Jaundice in Heart Failure without Pulmonary Infarction.*—The occurrence of frank jaundice in cases of myocardial failure without pulmonary infarction is extremely rare. In 273 cases of congestive heart failure not complicated by pulmonary infarction, frank jaundice occurred only once, an incidence of 0.36 per cent. In this instance acute rheumatic fever was complicated by a large pericardial

TABLE 1.—Incidence of Clinical Jaundice and Its Relation to Pulmonary Infarction in the Various Types of Heart Disease

Type of Heart Disease	Total Number of Cases	Without Pulmonary Infarction		With Pulmonary Infarction	
		Number of Cases	Cases with Jaundice	Number of Cases	Cases with Jaundice
Rheumatic with valvular defects.....	165	88	1	77	11
Coronary artery thrombosis.....	95	65	0	33	2
Endocarditis, bacterial.....	53	42	0	11	1
Heart failure, right*.....	43	33	0	10	0
Syphilitic.....	32	24	0	8	1
Miscellaneous.....	36	12	0	12	1
Total.....	424†	273	1	151	16

\* The group of cases listed under the heading of right heart failure are those due to chronic pulmonary disease, kyphoscoliosis, etc.  
† The incidence of frank jaundice in cases of pulmonary infarction was 10.6 per cent, and in cases without pulmonary infarction only 0.3 per cent.

effusion compressing both lungs and acute gastritis and duodenitis as well as by acute inflammatory lesions of the coronary arteries, aorta, pulmonary artery and veins of the liver.

*Absence of Frank Jaundice in Pulmonary Infarction of Noncardiac Diseases.*—Thirty cases of pulmonary infarction were noted at necropsy in subjects without heart disease. In the main the infarcts were embolic in origin, complicating surgical procedures, malignant disease or peripheral infections. In no instance was clinical jaundice observed. In 9 cases the infarcts were necrotic or infected. Pleuritis complicated 2 cases and bronchopneumonia 2 others. Passive congestion of the liver was present in 9 cases. Evidence of central atrophy or necrosis was observed in 6 cases. These observations indicate that pulmonary infarction alone does not cause clinical jaundice.

5. Jolliffe, N.: Liver Function in Congestive Heart Failure, J. Clin. Investigation 8:419, 1930.

*Significance of the Size, Number, Location and Age of Pulmonary Infarcts.*—There does not appear to be any difference in these factors in the 16 patients with jaundice and the 134 nonjaundiced subjects with pulmonary infarction. In 5 cases of marked jaundice a solitary infarct in the lower lobe of the right lung was present. Multiple infarcts of the lung were present in the remaining 11 cases (70 per cent).

In the 134 cases without clinical jaundice, the number of solitary and of multiple infarcts was as follows:

	Solitary Infarcts		Multiple Infarcts
	No. Cases	Lobe	
Rheumatic cardiovalvular diseases (65 cases)	11	RLL	42
	5	LLL	
	4	RML	
	2	RUL	
	2	LUL	
	2	LUL	
Coronary thrombosis (31 cases)	5	RLL	22
	3	LLL	
	1	RUL	
Right heart failure (10 cases)	2	LLL	5
	1	RLL	
	1	RUL	
	1	LUL	
Bacterial endocarditis (10 cases)	5	LLL	5
Syphilitic heart disease (7 cases)	2	RLL	5
Miscellaneous group (11 cases)	2	RUL	6
	1	RLL	
	1	LLL	
	1	LUL	

Eighty-five patients, or 63 per cent, had multiple infarctions in comparison with 70 per cent in the group with jaundice. Solitary infarcts occurred in the right lung in 37 per cent, as compared to 30 per cent in the patients with jaundice. There was a definitely greater frequency of infarction in the right lung. No difference in the size of the infarcts could be discerned in jaundiced as contrasted with nonjaundiced subjects. Old infarcts were present too infrequently (5 times in the entire series) to be of significance.

*Infection of Infarcts.*—Infection of infarcts occurred in 7 per cent of 135 cases without jaundice as compared to 25 per cent of 17 cases with jaundice. A complicating infection may therefore play a contributory rôle in the production of jaundice.

#### CONGESTIVE HEART FAILURE AS A FACTOR IN THE INCIDENCE OF CLINICAL JAUNDICE

An analysis of our data as to the duration and the type of heart failure indicates that this factor is of prime importance in the causation of clinical jaundice in cardiac disease. In estimating the onset and

degree of heart failure, definite criteria were adopted to render the data reliable. Orthopnea, dependent edema, ascites and hydrothorax in the clinical history were accepted as evidence of the existence of congestive heart failure.

*Degree of Heart Failure.*—No difference in the degree of the heart failure during the last illness was noted in those patients who were jaundiced and those who were not.

*Duration of Heart Failure.*—The duration of heart failure was classified as (1) acute or recent (less than a week), (2) less than four months and (3) more than four months.

In patients with rheumatic cardiovalvular disease the duration of the heart failure seemed to be the most important determining factor. Among those without jaundice 40 per cent suffered from acute heart failure, 54 per cent had shown failure less than four months, and 6 per cent for more than four months. In contrast, no patient with cardiac jaundice had died in acute heart failure, 46 per cent had suffered from circulatory failure for less than four months, and 54 per cent for more than four months.

Sixty-four per cent of the patients with heart failure uncomplicated by pulmonary infarction had died of acute heart failure; 30 per cent had suffered from heart failure for less than four months and 6 per cent for more than four months. The highest incidence of acute failure occurred in patients with coronary thrombosis and bacterial endocarditis (80 and 81 per cent respectively), the groups which presented the lowest incidence of jaundice and pulmonary infarction.

It is evident from these observations that the duration of congestive heart failure and of pulmonary congestion is a decisive factor in determining whether frank jaundice will develop, especially in cases of rheumatic cardiovalvular disease.

*Type of Heart Failure.*—Among 43 cases of primary failure of the right side of the heart due to chronic pleuropulmonary disease, kyphoscoliosis and similar conditions there was not a single instance of clinical jaundice despite the fact that the duration of heart failure corresponded closely to that in the cases of rheumatic cardiovalvular disease. In this group, pulmonary infarction was relatively infrequent. The degree and duration of congestion in the pulmonary circulation may therefore be an important element in the causation of jaundice, as well as of pulmonary infarction, in heart disease.

An analysis of the cases of coronary thrombosis (95 cases) lends support to this deduction. In the 2 instances in which jaundice was observed in coronary thrombosis, long-standing previous injury of the anterior descending branch of the left coronary artery (at least six months) had existed before the final occurrence of the recent thrombosis which caused the terminal heart failure. In both cases, chronic



passive congestion of the lungs was present. In 4 cases of coronary thrombosis complicated by pulmonary infarction and long-standing heart failure, jaundice did not develop. In 2 cases with thrombosis of the right coronary artery alone, and in 7 others accompanied by closure of the left coronary artery and pulmonary infarction, clinical jaundice did not occur. These facts speak against the importance of acute and chronic passive congestion of the liver, *per se*, as the essential cause of jaundice in heart disease.

#### RELATION OF PATHOLOGIC ALTERATION IN THE STRUCTURE OF THE LIVER TO CARDIAC JAUNDICE

Oertel<sup>6</sup> was the first to note "noninflammatory necroses" of the liver in cases of clinical jaundice and cyanosis. Pulmonary infarctions were present in his cases but were not stressed by him. More recently the pathogenesis of the pericentral lesions of the liver lobule have been more definitely defined.<sup>7</sup>

We have compared the anatomic alterations in the liver in various types of heart disease with and without pulmonary infarction and with and without jaundice. These hepatic lesions were classified as (1) chronic passive congestion, (2) pericentral atrophy or fibrosis, (3) pericentral necrosis, (4) inflammatory lesions and (5) cirrhosis of the liver.

Anatomic damage to the liver was found in all of the 17 jaundiced patients. In 3, chronic hyperemia was the sole lesion. Hyperemia was combined with pericentral atrophy or fibrosis and necrosis in 10 cases. Pericentral atrophy alone was present in 3 cases. One patient had what might be characterized as a true cardiac cirrhosis. Three had marked hemorrhages in the hepatic parenchyma. In another case a diffuse endophlebitis, possibly on a rheumatic basis, was present without atrophy or necrosis of the central lobule. A classification of the lesions and their relationship to the presence or absence of jaundice or of pulmonary infarction is presented in table 2.

Of 127 cases with pulmonary infarction but without jaundice, the liver was normal microscopically in 6 (5 per cent). Thirty-six cases (27 per cent) showed chronic passive congestion alone. Sixty-two cases (50 per cent) presented congestion and also central atrophy and necrosis. Twenty-three cases (18 per cent) showed central atrophy alone. A case of subacute bacterial endocarditis showed only focal round cell infiltrations. A case of coronary thrombosis showed a fatty liver.

6. Oertel, H.: A Further Contribution to the Knowledge of Multiple Non-Inflammatory Necrosis of the Liver with Jaundice (*Hepar Necroticum cum Ictero*) *J. Exper. Med.* 8:103, 1906.

7. Zimmerman, H. M., and Hillsman, J. A.: Chronic Passive Congestion of the Liver, *Arch. Path.* 9:1154 (June) 1930.

A significant difference in the distribution of anatomic lesions between the jaundiced and the nonjaundiced groups with pulmonary infarction is noted in the the greater incidence of combined lesions of chronic passive congestion, central atrophy and necrosis in the former group. Eighty-three per cent of the jaundiced group presented the combined lesions of chronic passive congestion, central atrophy and necrosis,

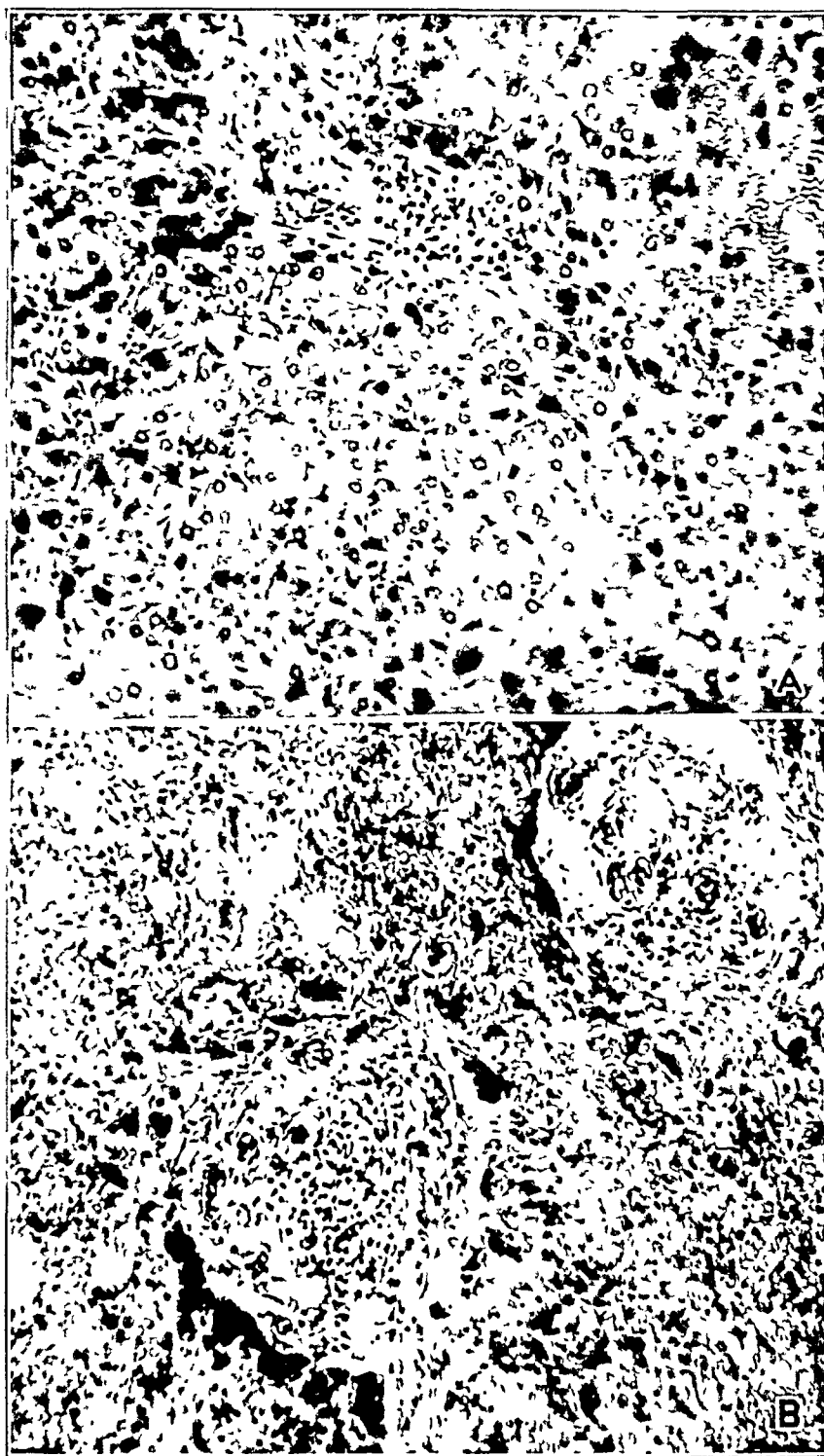
TABLE 2.—*Relative Incidence of Anatomic Lesions in the Liver in Various Types of Heart Disease*

<i>A. Without Jaundice, with or without Pulmonary Infarction</i>					
Type of Heart Disease	Anatomic Lesions	With Infarction		No Infarcts	
		Number of Cases	Per Cent	Number of Cases	Per Cent
Rheumatic with valvular defects.	Absent	2	3	3	3
	C. P. C.*	16	25	33	44
	C. A.	11	18	12	16
	C. P. C., C. A., Nec.	34	54	28	37
Coronary artery thrombosis.....	Absent	3	10	4	9
	C. P. C.	9	29	26	57
	C. A.	4	13	6	13
	C. P. C., C. A., Nec.	15	48	10	21
Endocarditis, bacterial.....	Absent	1	10	10	30
	C. P. C.	3	30	15	45
	C. A.	3	30	4	12.5
	C. P. C., C. A., Nec.	3	30	4	12.5
Heart failure, right.....	Absent	0	0	0	0
	C. P. C.	2	25	12	52
	C. A.	1	12.5	5	22
	C. P. C., C. A., Nec.	5	62.5	6	26
Syphilitic.....	Absent	0	0	1	8
	C. P. C.	2	29	4	30
	C. A.	4	57	1	8
	C. P. C., C. A., Nec.	1	14	7	54
Miscellaneous.....	Absent	0	0	0	0
	C. P. C.	4	50	7	70
	C. A.	0	0	2	20
	C. P. C., C. A., Nec.	4	50	1	10
<i>B. With Clinical Jaundice, with or without Pulmonary Infarction</i>					
Type of Heart Disease	Anatomic Lesions	With Infarction		No Infarcts	
		Number of Cases	Per Cent	Number of Cases	Per Cent
17 cases of various types of heart disease	Absent	0	..	..	..
	C. P. C.	3	18	1	..
	C. A.	3	18	..	..
	C. P. A., C. A., Nec.	10	64	..	..

\* C. P. C. indicates chronic passive congestion; C. A., central atrophy; Nec., necrosis.

whereas anatomic lesions of this severity were present in only 43 per cent of the total series of cases of heart disease without jaundice.

In heart failure without pulmonary infarction (234 cases) the liver was normal in twice as many cases (9 per cent compared with 5 per cent in the cases of infarction without jaundice), and only approximately a third as many showed combined lesions of the liver (26 per cent compared with 83 per cent).



Photomicrographs showing lack of correlation between anatomic lesion in liver and intensity of clinical jaundice: *A*, section from the liver in the case with the greatest intensity of jaundice in the series (bilirubin content of blood, 8 mg. per hundred cubic centimeters; icterus index, 150). The liver shows only relatively slight changes. *B*, section from a case in which the bilirubin content was 1 mg. Note the extensive parenchymal changes as compared to those shown in *A*.

It is evident that clinical jaundice in heart disease is associated generally with marked pathologic alterations in the parenchyma of the liver. However, in individual cases one cannot predict the degree of jaundice by an examination of microscopic sections of the liver. In the case which clinically showed the most intense jaundice the anatomic changes in the liver were comparatively slight, in fact less marked than in most of the cases without jaundice (fig.). It is therefore not always possible to correlate the degree of structural alteration and the functional derangement of the liver.

#### FUNCTION OF THE LIVER IN HEART DISEASE

A disturbance in the metabolism of blood pigment has been repeatedly demonstrated in congestive heart failure. The most constant findings are urobilinogenuria<sup>8</sup> and urobilinuria.<sup>9</sup> This has been attributed to increased destruction of blood because deposits of hemosiderin are to be seen in the lungs.<sup>10</sup> A test of tolerance for water and exercise has elicited urobilinuria in latent heart failure.<sup>11</sup> Bilirubin excretion tests, measuring the capacity of the liver to remove bilirubin administered parenterally, show a diminution of this function in heart failure.<sup>12</sup> A metabolic test based on the capacity of the liver to oxidize cinchophen under standardized conditions also showed altered function in cases of congestion of the liver.<sup>13</sup>

A thorough study of the function of the liver was recently reported by Jolliffe<sup>5</sup> in 16 subjects with congestive failure, some with clinical jaundice. Urobilinogen, serum bilirubin, bromsulphalein excretion and levulose tolerance tests were carried out at frequent intervals. In 93 per cent of the 16 cases some alteration in the function of the liver was noted. No characteristic type of dysfunction was found in chronic passive congestion of the liver. In only a single person were all four tests abnormal. In individual cases no parallelism between the degree of heart failure and the impairment of hepatic function could be noted. One patient suffering from most marked congestive heart failure, which ended fatally, showed no evidence of hepatic dysfunction accord-

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8. Wallace, G. H., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch. Int. Med.* **35**:698 (June) 1925.

9. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, *J. A. M. A.* **91**:1768 (Dec. 8) 1928.

10. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, *J. A. M. A.* **80**:1516 (May 26) 1923.

11. Adlercreutz, E.: Urobilinuri efter vätskebelastning och kroppsrörelse vid kompenserade hjärtfel, *Finska läk.-sällsk. handl.* **72**:974, 1930.

12. Eilbott, W.: Funktionsprüfung der Leber mittels Bilirubinbelastung, *Ztschr. f. klin. Med.* **56**:529, 1927.

13. Lichtman, S. S.: Cinchophen Oxidation Test of the Function of the Hepatic Cells, *Arch. Int. Med.* **48**:98 (July) 1931.

ing to these tests. Fishberg<sup>10</sup> and Ottenberg, Rosenfeld and Goldsmith<sup>14</sup> observed some retention of tetrachlorphenolphthalein in the majority of cases of congestive heart disease due to faulty excretion by the liver.

Since the present study was not primarily a study of the function of the liver in heart disease, only routine observations are available. Qualitative and quantitative studies with the van den Bergh test were usually made, but bromsulphalein excretion tests and determinations of the icterus index were made in only a few instances.

Laboratory observations were made in 15 of 17 cases of cardiac jaundice. The serum bilirubin varied between 0.5 and 8 mg. per hundred cubic centimeters. In 12 of the 15 cases it exceeded 2 mg. Of 11 cases in which a qualitative van den Bergh test was made, a prompt positive result was present in 10. The remaining case gave a direct delayed reaction. Bilirubinuria was present in all the cases with jaundice. An icterus index of 110, 120 and 150 on three tests was obtained in a case which on two occasions showed a serum bilirubin content of 8 mg. per hundred cubic centimeters with a prompt positive direct van den Bergh reaction. The two cases with the highest serum bilirubin readings (8 mg. per hundred cubic centimeters) were cases of mitral stenosis and of coronary thrombosis, respectively.

In 21 instances of heart disease with pulmonary infarction but without clinical jaundice the serum bilirubin was determined. In 13 cases normal values, below 0.35 mg. per hundred cubic centimeters, were recorded. Latent icterus, the bilirubin varying between 0.6 and 2 mg., was present in the remaining 8 cases. An indirect van den Bergh reaction was present in all instances except in a case which gave a delayed direct reaction with 0.35 mg. of bilirubin.

In 2 cases of heart failure with pulmonary infarction, one with, and the other without, jaundice there was a bromsulphalein dye retention in the blood of 15 per cent in thirty minutes. A case of mitral and tricuspid insufficiency without jaundice showed a serum bilirubin of 0.6 mg. per hundred cubic centimeters and bile in the urine on two occasions. In the case in which jaundice was present the 15 per cent retention was recorded during the phase of recovery.

The icterus index was determined in 6 cases of heart disease with pulmonary infarction but without jaundice. Normal readings of 5 and 6 were obtained in 3 cases. Latent icterus, indicated by readings of 9, 12 and 15, was shown in the remaining 3 cases.

From the foregoing data, it is evident that in heart failure with jaundice the degree of retention of bilirubin in the blood may approach

14. Ottenberg, R.; Rosenfeld, S., and Goldsmith, L.: The Clinical Value of the Serum Tetrachlorphenolphthalein Test for Liver Function, *Arch. Int. Med.* **34**: 206 (July) 1924.

that found in obstruction of the common bile duct and the quantitative van den Bergh reaction may equal that seen in a "regurgitation" type of jaundice (Rich). Advanced degrees of heart failure may exist, however, without retention of bilirubin in the blood.

#### RENAL FUNCTION IN RELATION TO OCCURRENCE OF JAUNDICE IN HEART DISEASE

The occurrence of azotemia in the course of advanced heart failure is commonly observed. When circulatory stasis is superimposed on a previously damaged kidney, uremia may supervene. A reciprocal relationship between excretion of certain substances by the liver and by the kidney has been noted. In the presence of retention of bilirubin due to failure of excretion of this substance by the liver, the kidney may assume the burden of excretion. This has been noted by Hanner and Whipple<sup>15</sup> in studying excretion of phenolsulphonphthalein in the urine in the presence of experimental injury to the liver in dogs. Resnick and Keefer<sup>16</sup> made a similar experimental observation when studying the causation of jaundice in heart disease. We therefore tried to observe whether the retention of nitrogenous substances in the blood affected the incidence of clinical jaundice.

In the jaundiced group only a single case showed evidence of renal impairment as measured by a retention of urea nitrogen in the blood of 32 mg. per hundred cubic centimeters. There were 11 nonjaundiced patients in whom the urea nitrogen of the blood varied between 25 and 95 mg. per hundred cubic centimeters. The renal factor does not, therefore, appear to be significant.

#### FORMATION AND RESORPTION OF BILIRUBIN

It has been demonstrated repeatedly that localized extravasations of blood, spontaneous or artificially produced, rarely cause bilirubinemia despite the fact that bilirubin is formed locally.<sup>17</sup> For final

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15. Hanner, J. P., and Whipple, G. H.: The Elimination of Phenolsulphonphthalein by the Kidney. The Influence of Pathologic Changes in the Liver, *Arch. Int. Med.* **48**:598 (Oct.) 1931.

16. Resnik, W. H., and Keefer, C. S.: Jaundice Following Pulmonary Infarction in Patients with Myocardial Insufficiency: II. An Experimental Study, *J. Clin. Investigation* **2**:389, 1926.

17. van den Bergh, A. A. H., and Snapper, I.: Untersuchungen über den Icterus, *Berl. klin. Wchnschr.* **51**:1180, 1924. Whipple, G. H., and Hooper, G. W.: Icterus. A Rapid Change of Hemoglobin to Bile Pigment in the Pleural and Peritoneal Cavities, *J. Exper. Med.* **23**:137, 1916. Rich and Resnik.<sup>1</sup> Ohno, Yukizo: Zur Frage der Pathogenese des Ikterus, *Med. Klin.* **23**:1577, 1927. Aschoff, L.: Ueber Bildungs-und-Ausscheidungsstörungen der gallenfähigen Substanzen besonders des Gallenfarbstoffs, *Acta path. et microbiol. Scandinav.* **5**:338, 1928. van den Bergh, A. A. H., and Snapper, I.: Ueber anhepatische Gallenfarbstoffbildung, *Berl. klin. Wchnschr.* **52**:1082, 1915.

acceptance of such work, it must be proved that the local extravasation of red blood cells has undergone conversion to bilirubin, and that the bilirubin has not been reduced to urobilinogen by local bacterial action or anoxemia<sup>18</sup> before absorption into the blood stream. The demonstration of bilirubin crystals in hematomas<sup>19</sup> furthermore indicates that under certain conditions this substance is insoluble. As serum is an excellent solvent of bilirubin, Ottenberg<sup>20</sup> has explained the eccentric distribution of jaundice in the presence of edema reported by Meakins and Page<sup>21</sup> on the basis of the low protein content of edema fluids.

In our opinion, local hemolysis in the lung is a factor of paramount importance. There is experimental evidence to indicate that after repeated injections of blood into the bronchial tree, hemolysis occurs instead of phagocytosis of the fragmented erythrocytes.<sup>22</sup> Only after repeated injections did Maugeri<sup>23</sup> note a significant increase in serum bilirubin. In unpublished observations Fried<sup>24</sup> was also able to demonstrate bilirubinemia by producing pulmonary hematomas in two dogs.

Absorption of fluids from the lungs and pleural cavity takes place rapidly. The classic studies of Nothnagel<sup>25</sup> and Fleiner<sup>26</sup> on the absorption of corpuscular elements of blood from the bronchial tree and pleural cavity indicate that the lymphatics convey the intact cells to the lymph node filters. The thoracic duct usually contained few erythrocytes. Investigation of pathologic material associated with recent antemortem hemorrhage into the lung confirmed the very rapid removal of interstitial hemorrhages. In the presence of disease of the mediastinal lymph nodes, as in tuberculosis and other chronic infections, however, obstruction to removal of corpuscular elements was evident. In such instances the resorption was delayed or prevented.

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18. Rabinowitch, I. M.: *The Origin of Urobilinogen: Clinical Experiment*, Arch. Int. Med. **46**:1014 (Dec.) 1930.

19. Virchow, R.: *Die pathologischen Pigmente*, Virchows Arch. f. path. Anat. **1**:379, 1847.

20. Ottenberg, R.: *Jaundice in Heart Disease*, in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932, vol. 3, p. 917.

21. Meakins, J.: *Distribution of Jaundice in Circulatory Failure*, J. Clin. Investigation **4**:135, 1927. Page, I. H.: *Ipsilateral Edema and Contralateral Jaundice Associated with Hemiplegia and Cardiac Decompensation*, Am. J. M. Sc. **177**:273, 1929.

22. Briscoe, J. C.: *An Experimental Investigation of the Phagocytic Action of Alveolar Cells of the Lung*, J. Path. & Bact. **12**:66, 1908.

23. Maugeri, S.: *Die pulmonogene Entstehung des Ikterus*, Beitr. z. path. Anat. u. z. allg. Path. **86**:375, 1931.

24. Fried, B. M.: Personal communication.

25. Nothnagel, H.: *Zur Resorption des Blutes aus dem Bronchialbaum*, Virchows Arch. f. path. Anat. **71**:414, 1877.

26. Fleiner, W.: *Ueber die Resorption corpusculärer Elemente durch Lungen und Pleura*, Virchows Arch. f. path. Anat. **97**:112 and 282, 1888.

A correlation of the factors of local hemolysis and increased activity of the reticulo-endothelial system furnishes, we believe, optimum conditions for the rapid formation of bilirubin. Under the optimum conditions for the solubility of this bilirubin, fluids are absorbed at a rapid rate from the lung tissue.

#### RÔLE OF SYSTEMIC AND LOCAL PULMONARY INFECTION

The enhanced activity of the reticulo-endothelial system which attends infection<sup>27</sup> may play a prominent rôle in the genesis of jaundice. For this reason we analyzed our material for the presence of infection. We depended on anatomic evidence of infection rather than on fever and leukocytosis alone.

The types of infection encountered were as follows: (1) infection and necrosis of pulmonary infarcts; (2) pleuritis, the result of exten-

TABLE 3.—*Incidence of Systemic or Pleuropulmonary Infection in Heart Disease in Relation to Pulmonary Infarction and Jaundice*

Type of Infection	Without Jaundice with Infarct (151 Cases) per Cent	With Jaundice (17 Cases) per Cent
Infection of infarct.....	7.0	25
Pleuritis.....	2.0	12
Bronchopneumonia.....	11.0	25
Empyema.....	0.0	6
Acute rheumatic fever*.....	31.0	50
Hemolytic streptococcemia.....	0.0	6
Average.....	8.5	20

\* Incidence only in the group with rheumatic cardiovalvular disease.

sion of pulmonary infarcts to the surface of the lung; (3) empyema, the result of secondary infection of infarcts or effusions; (4) bronchopneumonia, and (5) systemic infections, such as acute rheumatic fever and hemolytic streptococcemia. A comparison of the results in the cases with and without jaundice is shown in table 3. In the cases in which jaundice was present infection in one form or another occurred more than twice as frequently (20 to 9 per cent).

#### SUMMARY AND CONCLUSION

Two factors, the duration and the type of myocardial failure, are mainly responsible for the occurrence of pulmonary infarction. The lowest incidence of infarction occurred in patients with subacute bacterial endocarditis, in whom congestive heart failure rarely occurs, and in those with primary failure of the right side of the heart, in whom the left side is usually competent until the end. The highest incidence occurred in the group with rheumatic cardiovalvular disease, mostly in

27. Sacks, B.: The Reticulo-Endothelial System, *Physiol. Rev.* **6**:504, 1926.



those with disease of the mitral valves. This group also showed a longer duration of heart failure. Long standing pulmonary congestion, therefore, is a significant factor in the causation of pulmonary infarction, confirming the early experimental observations of Karsner and Ashe.<sup>28</sup>

The data indicate that jaundice is not directly correlated with the degree of anoxemia induced by pulmonary infarction. If it were true that the occurrence of frank jaundice depended wholly on the existence of an advanced degree of anoxemia, a much higher incidence of jaundice would occur in the cases of multiple and massive infarctions and of lobar pneumonia. Yet the existence of a pulmonary infarct appears to be an almost indispensable factor in the causation of clinical jaundice, occurring in 94 per cent of the cases. However, a combination of circumstances and factors is necessary.

In addition to long-standing pulmonary congestion, a higher incidence of anatomic lesions of the liver and of systemic or pulmonary infection is found in the cases with jaundice. A survey of the anatomic lesions of the liver and studies of the function of the liver make it apparent, however, that unless true cardiac cirrhosis or diffuse inflammatory vascular disease of the liver exists the jaundice is not primarily hepatogenous.

Infection, systemic or pleuropulmonary, also plays an important contributory rôle, probably by influencing the rate of formation and resorption of bilirubin from its source, the pulmonary infarct, and the rate of its excretion by the liver.

These clinical and anatomic observations lead us to the following concept of the probable mechanism responsible for frank jaundice in heart failure: In a patient with long-standing pulmonary stasis due to cardiac insufficiency, pulmonary infarction occurs. From this rich source, hemoglobin is made available by destruction and hemolysis of red blood cells, and bilirubin is rapidly formed. The presence of serum in the lung, owing to congestion and often to infection, facilitates the solution and absorption of the bilirubin. The capacity of the liver to excrete this substance is impaired, owing to anoxemia and to the toxic effect of infection on the parenchyma of the liver. However, unless extensive disease of the liver, i. e. true cirrhosis, is present, the causation of the frank jaundice is primarily pulmonogenic. The deleterious effects of anoxemia and of infection on the liver cells play a necessary but only a secondary rôle. The pulmonic factors of primary importance are the duration and type of heart failure, i. e., prolonged failure of or obstruction in the left side of the heart and pulmonary congestion, and the local factors favoring the rapid formation and absorption of bilirubin, i. e., pulmonary infarction, hemolysis of erythrocytes and local or systemic infection.

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28. Karsner, H. T., and Ashe, J. E.: Studies in Infarction: XI. Experimental Bland Infarction of the Lung, *J. M. Research* **22**:205. 1912-1913.

# PREMATURE LEFT VENTRICULAR BEATS FROM ELECTRICAL STIMULATION OF EXPOSED HUMAN HEART

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The value of the study of the excitatory process in the exposed human heart by Barker, Macleod and Alexander<sup>1</sup> is unquestioned. Their observations on electrically induced extrasystoles are of special interest. The deflection of Q-R-S in the three leads took direction according to a semblance of an orderly manner, when considered in relation to the many points stimulated. This direction of Q-R-S in the three leads corresponds to that which is frequently observed clinically and which is not readily understood according to the classic explanation. The result is that at present extrasystoles are not accurately localized with regard to their site of origin.

The work of Barker will probably be a forerunner of a proved pattern whereby one will be able to compare the electrocardiogram of extrasystoles from a patient with those from known sources in the human heart, and to make an accurate statement as to their site of origin.

Opportunities for such studies are not frequently available. Marvin and Oughterson<sup>2</sup> recently confirmed a part of the original observations. We are herewith presenting further evidence, from a different part of the heart than is shown in the original observation, in a third instance of a study of the form of ventricular extrasystoles in the exposed human heart.

Through Dr. Edwin M. Miller of the Presbyterian Hospital of Chicago, we were informed of the presence of a patient, 4 years of age, at the Chicago Municipal Contagious Disease Hospital, in whom a purulent pericardial effusion developed following influenza of the upper respiratory tract. Dr. Miller had performed a pericardiotomy through the left half of the sternum at the levels of the fourth and fifth ribs.

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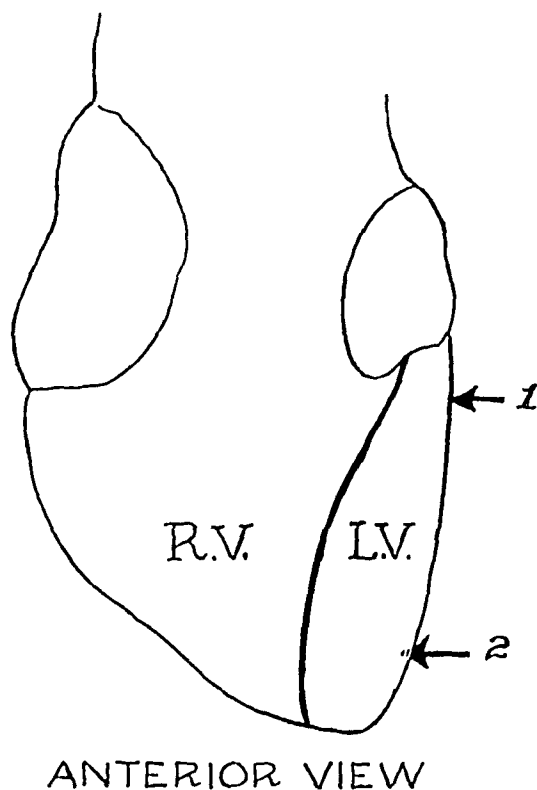
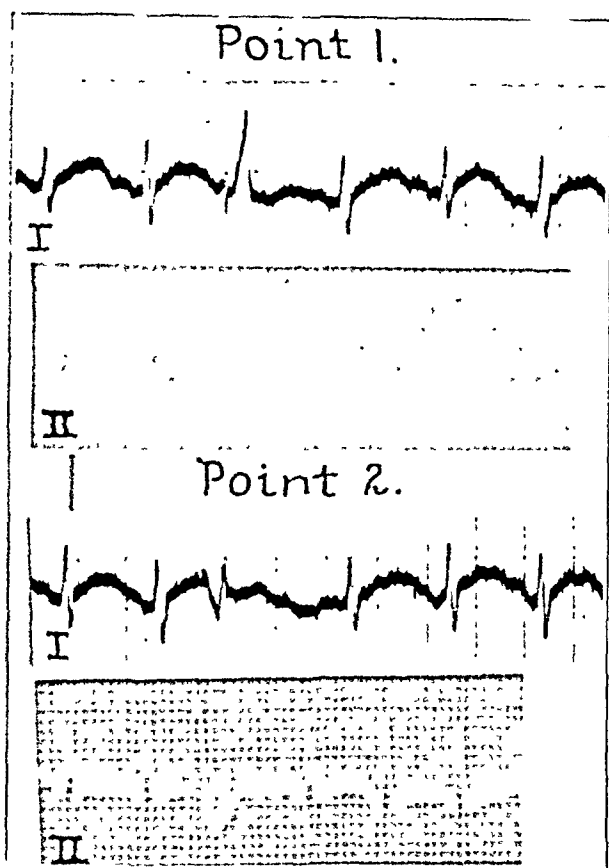
From the Department of Medicine, Rush Medical College, The University of Chicago and the Municipal Contagious Disease Hospital.

1. Barker, P. S.; Macleod, A. D., and Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, *Am. Heart J.* **5**:720 (Aug.) 1930.

2. Marvin, H. M., and Oughterson, A. W.: The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, *Am. Heart J.* **7**:471 (April) 1932.

Through the operative wound could be seen the left auricular appendix and the basal portion of the left side of the ventricles. With the permission of Dr. A. L. Hoyne, we were permitted to elicit electrically excited extrasystoles from this heart.

The method used was the same as that of Barker, except that we observed only leads I and III simultaneously, and we used only about 6 volts of current. Mr. F. V. Schaal, of the Cambridge Instrument Company, allowed us to use a portable electrocardiograph, and he assisted in its operation at the time of the experiments.



Results from stimulation of *points 1* and *2*. In *point 1*, leads I and III were recorded simultaneously. The main deflections are discordant: up in lead I and down in lead III. In *point 2*, leads I and III were recorded simultaneously. The main deflections are discordant: down in lead I and up in lead III. The diagram at the right is of the anterior surface of the heart. *Point 1* is at the posterior lateral margin near the base of the left ventricle. *Point 2* is near the apex on the posterior surface of the left ventricle near the posterior lateral border.

Two points were stimulated along the left border of the heart, both in the left ventricle. The first point was near the base (accompanying figure) on the lateral posterior margin. The second point was near the apex (fig.) on the posterior surface near the left lateral margin. The first point of stimulation was visible; the second was not. The intraventricular septum was located by the anterior descending branch of the left coronary artery, and, in addition, the septum was seen to

remain as a firm band between the bulging and relaxed walls of both ventricles during diastole. We believe that there is no question but that in both instances the left ventricle was stimulated.

The results are shown in the accompanying figure. In both electrocardiograms the curves are discordant. When the left ventricle was stimulated near the base, the main deflection of Q-R-S was upright in lead I and inverted in lead III. When the left ventricle was stimulated near the apex, the main deflection of Q-R-S was inverted in lead I and upright in lead III. Stimulation of other points was not done because of the condition of the patient, who died twenty-two days after these observations were made. Postmortem examination was not obtained.

#### COMMENT

Our curves differ in detail from those of Barker and his co-workers, because they were derived from different sites. Our basal stimulation (our point 1) was on the lateral posterior surface of the left ventricle, to the left of Barker's point 11, and the entire width of the heart posteriorly when compared with his point 1. The distance from the apex or base puts our point 1 at about the same level as Barker's points 1 and 11.

Our apical stimulation (our point 2) is in a similar location to the point B of Marvin and Oughterson's<sup>2</sup> observations (fig. 3, p. 474). As may be seen, the resulting electrocardiograms are similar.

Such observations as these and the works cited may result in the establishment of a chart or pattern whereby one will be able to compare extrasystoles as they occur in patients with those from known sources in the human heart, and to make an accurate statement as to their site of origin. Such observations may also shed light on the controverted question of the significance of ventricular extrasystoles and may attach prognostic importance to those from certain regions.

#### CONCLUSIONS

1. Electrically induced extrasystoles from the base and apex of the human left ventricle gave discordant Q-R-S complexes; the extrasystole arising from the base was upright in lead I and inverted in lead III; that arising from the apex was inverted in lead I and upright in lead III.

2. The ventricular extrasystole elicited from our point 1 is from a region heretofore unexplored.

3. The ventricular extrasystole elicited from our point 2 corresponds to and confirms one observation made by Marvin and Oughterson.

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# INFLUENCE OF SCLEROTIC ARTERIAL WALL ON BLOOD PRESSURE MEASUREMENTS

REPORT OF CASE WITH CALCIFICATION OF ONE RADIAL ARTERY

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Many studies have been made to determine whether a markedly sclerotic artery requires considerably more pressure to obliterate its lumen than a normal soft artery. The results of these investigations, largely derived from studies made directly on excised arteries, support the view that the pressure of but a few more millimeters of mercury is required to obliterate the lumen of a calcified artery. These findings apparently have not been verified in the living person. A person who had a markedly sclerotic radial artery in one arm and a soft radial artery in the other arm would offer an opportunity for an answer to this question by a comparison of simultaneous readings of the blood pressure in both arms. We have recently observed such a person, and the results of studies on him are presented in this paper.

## REVIEW OF THE LITERATURE

An excellent summary of the literature on this subject is presented in the papers of MacWilliam and Kesson<sup>1</sup> and Janeway and Park,<sup>2</sup> to which one should refer for details. Analysis of the literature shows that the various studies may be divided into those made on excised "dead" arteries, those made on recently excised, presumably "living" arteries and studies on living patients. In the studies made on excised dead arteries, von Basch<sup>3</sup> and Martin<sup>4</sup> found that the lumen of the

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From the Medical Clinics of the New England Medical Center and Beth Israel Hospital, Boston.

1. MacWilliam, J. A., and Kesson, J. E.: The Estimation of Systolic Blood Pressure in Man, with Special Reference to the Influence of the Arterial Wall, *Heart* 4:279 (May 29) 1913.

2. Janeway, T. C., and Park, E. A.: An Experimental Study of the Resistance to Compression of the Arterial Wall, *Arch. Int. Med.* 6:586 (Nov.) 1910.

3. von Basch, S.: Der Sphygmomanometer und seine Verwerthung in der Praxis, *Berl. klin. Wchnschr.* 24:181, 1887.

4. Martin, C. J.: The Determination of Arterial Blood Pressure in Clinical Practice, *Brit. M. J.* 1:865 (April 15) 1905.

normal artery could be obliterated by a pressure of from 1 to 2 mm. of mercury, whereas a pressure of from 5 to 7 mm. was required to obliterate the lumen of calcified arteries. On the other hand, Herringham and Womack,<sup>5</sup> also working with excised "dead" arteries, found that a pressure of from 4 to 34 mm. of mercury was required to obliterate the lumen of calcified vessels. They found no correlation between the age of the person, the condition of the arterial wall and the pressure necessary for obliteration.

Investigations on excised "living" arteries, in general, have shown that the resistance of the vessel wall has no significant influence on the measurement of blood pressure. Janeway and Park<sup>2</sup> concluded that in the case of the normal large artery only a few millimeters of pressure were required for the obliteration of its lumen, and that calcified and thickened vessels were obliterated by a pressure of 20 mm. at the most, and usually of from but 10 to 15 mm. MacWilliam and Kesson<sup>1</sup> and MacWilliam and Melvin<sup>6</sup> found that relaxed living arteries with a normal or "thickened" wall offered but slight resistance to compression, usually not more than a few millimeters of mercury. Janeway and Park and MacWilliam, Kesson and Melvin showed that any artery the smooth muscle of which was contracted became extremely resistant to obliteration of its lumen by pressure, but that this state could be overcome quickly and easily by repeated compression and massage. In this way they explained the results of Herringham and Womack's studies on excised dead arteries, in which considerable pressure was required to obliterate the lumen of calcified arteries.

In addition to the foregoing studies made directly on excised arteries, observations on the living patient supply indirect evidence for the view that the uncontracted artery, whether normal or calcified, furnishes but little resistance to the obliteration of its lumen. Hensen,<sup>7</sup> in 1900, studied the blood pressure of a moribund patient with tuberculosis who, palpation showed, had moderate arteriosclerosis of the brachial artery. He found the systolic blood pressure as low as from 30 to 40 mm. of mercury, and therefore contended that since there was still some pressure of blood within the artery, the resistance of the arterial wall itself could not have exceeded 20 mm. of mercury. Dameshek and Loman<sup>8</sup> recently compared blood pressure readings as obtained by the usual

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5. Herringham, W. P., and Womack, F.: *Proc. Roy. Soc. Med. (Sect. Med.)* **2**:37, 1908.

6. MacWilliam, J. A., and Melvin, G. S.: *The Estimation of the Diastolic Blood Pressure in Man*, *Heart* **4**:393 (June 14) 1913.

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clinical method and by a direct intra-arterial method, and on the basis of indirect evidence they have concluded that a sclerosed artery introduces little if any error in measurements of the blood pressure. No roentgen studies of the arteries were made. Williamson<sup>9</sup> took into consideration the fact that arteriosclerosis is usually more marked in the lower extremities. In his studies, readings of the blood pressure were made in the arms and thighs of arteriosclerotic patients. Marked differences in the blood pressure could be demonstrated. These results cannot be interpreted satisfactorily, because the observer in this study did not determine by x-rays the condition of the arteries in his subjects, nor did he make simultaneous readings of the blood pressure in the arm and leg. Finally, Müller,<sup>10</sup> by direct determination of the venous pressure, indirectly concluded that the tension of the arterial wall averaged 12 mm. of mercury both in healthy adults and in patients with arteriosclerosis but without hypertension.

#### METHOD AND RESULTS OF PRESENT STUDY

The present study was prompted by the finding of an unusual clinical condition, namely, a markedly sclerotic and calcified radial artery in one forearm and a soft radial artery in the other arm.

P. K., a man, aged 64, entered the Observation Hospital of the New England Medical Center complaining of weakness and pallor of three years' duration. Most of his life he had done odd jobs, and he said that he had not especially used one arm more than the other for any period of time. He had been a waiter for less than a year. Examination revealed pallor of the mucous membranes and skin; a smooth, glistening tongue; absent vibratory sense in the lower extremities, and absence of free hydrochloric acid in the gastric juice after a subcutaneous injection of histamine. The hemoglobin was 56 per cent (Sahli), and the red blood count was 1,800,000 per cubic millimeter. A diagnosis of pernicious anemia, subacute combined sclerosis of the spinal cord and arteriosclerosis was made, and liver extract was given with a satisfactory response.

In the course of examination, it was noted that the right radial artery was markedly sclerotic and beaded and moderately tortuous. It could thus be felt over 7 cm. of its length. It was impossible to obliterate this pulse by digital compression, although the pressure of the manometer cuff on the arm or the forearm was easily able to do so. In contrast to this, the left radial artery was moderately soft, being just palpable against the radius. With compression of the brachial artery above systolic pressure, the left radial vessel could not be palpated at all. Both brachial arteries were markedly thickened on palpation, the right more than the left. The heart was of normal size clinically and radiographically. An electrocardiogram revealed no abnormality. Renal function tests were within normal limits. The blood calcium was 10.9 mg. per hundred cubic centimeters.

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9. Williamson, O. K.: Clinical Observations on the Influence of the Vessel Wall on (So-Called) Arterial Blood Pressure Readings, *Proc. Roy. Soc. Med. (Sect. Med.)* **2**:229 (April 27) 1909.

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Roentgenograms of the vessels of the upper extremities are shown in the accompanying figure. The widespread calcification of the vessels is easily observed, and it was found to be more marked in the lower extremities (plate not shown). Both brachial arteries were markedly calcified (plate not shown), the right more than the left. Both ulnar arteries were markedly calcified. The right radial artery likewise was calcified. A slight amount of calcification of the left radial artery could be made out at the level of the styloid process of the radius, a portion of the artery not utilized in this study. In spite of the taking of numerous other views of the left forearm in every possible position, the left radial artery could not otherwise be visualized by the x-rays.

Studies of the blood pressure were carried out in the following manner: First, readings of the blood pressure were obtained simultaneously over the brachial



Roentgenograms of the upper extremities of P. K. The right extremity is indicated by R; the left, by L.

arteries of both arms. The blood pressure cuffs were placed over both arms and connected by a T piece to a single mercury manometer. In this way, the blood pressure cuffs on both arms could be simultaneously inflated and deflated from the bulb on either arm. The patient was kept in a horizontal position, with both arms and the heart at the same level. Before making readings on both arms, both observers made simultaneous readings on one arm through a double stethoscope, in order to be certain that they used the same criteria for systolic and diastolic readings, and had the same acuteness of hearing. In making readings, the auscultatory method was used whenever possible. The first sounds heard on deflating the cuff were noted as systolic, even when they were not constant owing to respiratory variations. The beginning of the fourth phase was used as the criterion of diastolic blood pressure. In table 1, it is seen that both observers checked closely on many readings of the same side. Therefore, in simultaneous readings on both



TABLE 1.—*Simultaneous Readings of Blood Pressure of Left Brachial Artery, Made by Both Observers, Using a Double Stethoscope*

Date	Observer	Blood Pressure Readings	
		Systolic	Diastolic
3/17/32.....	D. A.	116	58
	A. K.	116	58
	D. A.	112	60
	A. K.	112	56
	D. A.	112	60
	A. K.	112	58
3/19/32.....	D. A.	120	64
	A. K.	120	64
	D. A.	132	64
	A. K.	132	64
	D. A.	132	64
	A. K.	132	64

TABLE 2.—*Simultaneous Readings of Blood Pressure on Right and Left Brachial Arteries in Patient with Sclerotic Right Radial and Soft Left Radial Artery*

Date	Observer	Right		Observer	Left	
		Systolic	Diastolic		Systolic	Diastolic
3/17/32.....	D. A.	118	66	A. K.	116	62
		116	64		114	60
		116	64		108	60
		116	60		108	62
	A. K.	118	64	D. A.	112	62
		112	66		110	62
		114	66		110	62
		118	66		116	62
	D. A.	106	62	A. K.	116	64
		110	64		112	66
		112	62		114	66
		112	62		114	66
	A. K.	108	64	D. A.	110	66
		112	62		114	64
		110	62		114	66
		110	62		114	66
3/23/32.....	D. A.	130	68	A. K.	126	68
		124	70		120	68
		124	70		118	70
		124	70		118	70
	A. K.	124	70	D. A.	122	70
		126	70		120	70
		122	72		122	72
		126	72		122	72
	D. A.*	122	72	A. K.	122	70
		118	70		118	68
		118	70		120	70
		118	70		120	70
5/22/32.....	D. A.	116	80	A. K.	126	86
		148	82		140	84
		142	84		144	84
		146	84		144	84
		146	84		142	84
		146	84		142	84
	D. A.	136	82	A. K.	136	78
		136	78		136	80
		132	78		128	78
		136	80		132	82
		136	88		134	88
		136	88		134	88
	A. K.	132	80	D. A.	130	80
		128	76		130	80
	A. K.	130	78	D. A.	130	78
		130	78		130	78
	Average of all readings.....		71			71

\* Patient sitting up with hands by sides.

arms, a leeway of 2 mm. at the most might be given to cover any possible error in reading the mercury. In table 2 are the readings made simultaneously on both arms, each observer shifting from one arm to the other after a series of two or more readings. In table 3 are the readings made over the radial vessels, with the

TABLE 3.—*Simultaneous Readings of Blood Pressure in Right and Left Radial Arteries, with Blood Pressure Cuffs on Forearms, in Patient with Sclerotic Right Radial Artery and Soft Left Radial Artery*

Date	Observer	Right		Observer	Left	
		Systolic	Diastolic		Systolic	Diastolic
3/17/32.....	A. K.	124	68	D. A.	118	66
		128	72		120	64
		124	76		124	68
		126	74		122	66
3/19/32.....	A. K.	128	*	D. A.	124	
		128			122	
		126			122	
	D. A.	124		A. K.	124	
		124			124	
	A. K.	126		D. A.	122	
		122			122	
		122			120	
	A. K.	144		S. H. P.	134	
		142			138	
		144			144	
		132			128	
		136			136	
		136			136	
	S. H. P.	136		A. K.	128	
		138			136	
		132			136	
	D. A.	118	†	A. K.	118	
5/22/32.....	D. A.	150		A. K.	148	
		142			146	
		144			140	
	D. A.	140		A. K.	132	
		138			134	
	A. K.	144		D. A.	140	
		146			138	
	A. K.	144		D. A.	138	
		142			138	
		142			138	
	Average of all readings.....		134			131

\* From this point all readings by palpation.

† Patient sitting up with arms by side.

blood pressure cuff over the lower part of each forearm. At first it was possible to use the auscultatory method over the radial arteries, but later it was found rather difficult to hear the sounds over the calcified radial artery, so that only the palpatory systolic readings were made. In general, it is seen that the systolic blood pressure at the radial artery by palpation was usually from 2 to 8 mm. more on the right (calcified) than on the left side, although the average showed a difference of only 3 mm. It is also seen that the average of all the readings of the radial arteries was about 10 mm. higher than those of the brachial arteries.

COMMENT

Clinically and radiographically, we are dealing with a patient who has in his right forearm a markedly sclerotic radial artery over its entire length, and in his left forearm a soft and only slightly thickened radial vessel. Both of the radial arteries seem to be of the same size. If both the radials were soft and uncalcified, we would expect approximately the same readings on both sides, for we have found bilateral simultaneous readings to be approximately the same in sixteen normal people who had normal blood pressure and soft radial arteries. We also found that simultaneous bilateral readings of the blood pressure in twenty patients with arteriolar hypertension showed no appreciable differences. If sclerosis of the radial artery causes little if any increase in the pressure necessary for obliteration of its lumen, we would expect little if any increase in the blood pressure on the right side. Actually, we found that of the thirty-one simultaneous readings of the blood pressure in the radial arteries of our patient, twenty-one showed readings from 2 to 10 mm. higher on the right side, and eight showed exactly the same readings on both sides. The average of all systolic readings of the right radial was 134 mm., while on the left side it was 131 mm. The tendency to slightly higher readings on the right (sclerotic) side, however, cannot be attributed to the sclerosis, for in similar studies on sixteen normal adults, we as well as others have found that for some unexplained reason the blood pressure was often slightly higher (from 2 to 6 mm.) on the right side. Blumgart and Ernstene<sup>11</sup> have suggested that since the right arm is usually larger than the left arm, the arteries in the right arm are probably larger than those in the left arm. Therefore, the flow of blood through any part of an artery of the right arm meets with slightly less resistance than through the corresponding part of the left arm. The result would be a slightly higher systolic blood pressure in the right arm. This idea is in keeping with Hering's<sup>12</sup> findings that the blood pressure is always lower in an atrophic arm than in a normal arm. If the foregoing is true, one would expect slightly higher blood pressure readings in the left arms of left-handed people. Practically all of our patients mentioned were right-handed, so that we are unable to verify that possibility with our material. Our evidence strongly supports the view that calcification of a vessel influences little, if at all, the reading of the blood pressure.

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There was one possible source of error in our study which we had to eliminate. This concerns the fact that in the left arm there is both a soft radial artery and a sclerotic ulnar artery. If, for a moment, we assume that a soft vessel requires much less pressure for the obliteration of its lumen than a sclerotic vessel, there is the possibility that in this case a cuff over the forearm might obliterate the soft radial artery at a pressure of, let us assume, 100 mm., while 120 mm. might be needed to obliterate the lumen of the sclerotic ulnar artery. In other words, at a pressure of 100 mm. there would be no flow of blood through the radial artery, but there would be a flow and pulse through the ulnar artery. The latter pulse might then be transmitted through the superficial and deep volar arches of the palm back to the radial artery distal to the cuff, thereby giving the examiner the impression that there was still a radial pulse, so that the retrograde pulse in the radial artery would be obliterated only when the ulnar pulse was also obliterated at a higher pressure.

In the present study we eliminated this possible error by simultaneously obstructing the flow through both ulnar arteries and then determining the radial pressures. The method used for compressing the ulnar arteries was as follows: Two pieces of steel were secured, each 21 by 5 by 0.4 cm. in size. These were wrapped in cotton batting and covered with adhesive plaster. With the forearms of the patient resting on a table about 15 cm. apart and with the volar surfaces upward, each end of one piece of steel was placed across the medial half of the volar surfaces of both wrists. The other piece of steel was placed under the medial half of the dorsa of both wrists, directly underneath the upper piece of steel. A blood pressure cuff was then wrapped around both pieces of steel which were between both hands. In this way a pressure up to 300 mm. of mercury could be exerted over both ulnar arteries. Then a blood pressure cuff was placed on each forearm above the steel and the radial pressures simultaneously determined as before. With the steel compressing the ulnar arteries at a pressure around 300 mm., it was inevitable that some of this pressure should be transmitted to the adjacent radial arteries, thus lowering the values obtained over the latter. This factor would, however, be the same on both sides. As table 4 indicates, the readings of the radial arteries on both sides were almost the same, although slightly lower than the readings without ulnar compression. The foregoing experiment, therefore, is additional evidence that the sclerotic vessel is not a significant factor in the determination of blood pressure with a sphygmomanometer.

Another aspect of our results is not so easily explained. A comparison of the readings in tables 2 and 3 indicates that apparently the systolic blood pressure in our patient's brachial arteries was almost invariably a little lower than in the radial arteries, the average of all readings showing the brachial pressure 10 mm. lower than the radial pressure. This is contrary to known physiologic studies on the normal animal and the human subject; viz., normally, the blood pressure is lower in the radial than in the brachial arteries. We studied the radial and brachial blood pressures of six normal subjects with normal blood pressure and soft radial arteries by palpation and five hypertensive patients with soft radial arteries by palpation, and we found that in all but one of them the radial blood pressure was invariably lower than, or the same as, that in the brachial artery (table 5). This indicates that our technic of determination of the blood pressure in the forearms

TABLE 4.—*Simultaneous Readings of Blood Pressure of Radial Arteries After Obstruction of Blood Flow Through Both Ulnar Arteries*

June 29, 1932						June 30, 1932			
Right Radial	Left Radial	Right Radial	Left Radial	Right Radial	Left Radial	Right Radial	Left Radial	Right Radial	Left Radial
118.....	120	120.....	130	120.....	122	107*.....	102†	84.....	84
118.....	120	122.....	134	128.....	124	104*.....	102†	106*.....	90
124.....	124	124.....	118	122.....	130	106*.....	106†	112*.....	94
94.....	130	118.....	112	135*.....	138†	106*.....	102†	112*.....	96
140.....	126								

\* Right ulnar artery not compressed.

† Left ulnar artery not compressed.

was satisfactory. In one of these subjects (case 11, table 5) who was the exception, a man of 64, with a blood pressure of 150 systolic and 88 diastolic, with soft radial arteries, the radial blood pressure was from 4 to 8 mm. higher than the brachial. We then studied similarly three subjects, aged 64, 72 and 73, respectively, in two of whom the radial and brachial arteries were markedly thickened and beaded, and in one of whom there was only a moderate degree of sclerosis. In all three cases the radial readings were higher than the brachial readings (table 5), and the greatest difference (80 mm.) was found in case 14, the subject with the most marked arteriosclerosis of the radial arteries.

It is difficult to explain these contradictory findings. Postmortem studies have shown that arteriosclerotic changes are more marked in the distal parts of the extremities, and in our patient this was true both clinically and by roentgen examination. However, our studies in this patient have shown that arteriosclerosis has no effect on the blood pressure readings. Therefore, a slightly higher blood pressure in our patient's radial than in his brachial arteries could not be due to this greater degree of arteriosclerosis in the periphery. Arteriosclerosis

TABLE 5.—*Blood Pressure Readings Simultaneously Made Over Both Brachial Arteries, Followed by Readings of Radial Arteries, then Brachial, Etc.; Eleven Subjects with Soft Radial Arteries and Three Subjects with Sclerotic Radial Arteries*

Age.....	Subjects with Soft Radials*										Subjects with Calcified Radials					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14		
	<div>R. L. 24</div>	<div>R. L. 26</div>	<div>R. L. 26</div>	<div>R. L. 27</div>	<div>R. L. 28</div>	<div>R. L. 51</div>	<div>R. 54</div>	<div>R. 55</div>	<div>R. 50</div>	<div>R. L. 60</div>	<div>R. L. 64</div>	<div>R. L. 55</div>	<div>R. L. 72</div>	<div>R. L. 72</div>		
Brachials.....	108 106 108 108 110 110 108 108	130 122 126 124 128 126 126 124	106 96 104 100 102 94	116 112 118 112 118 118 114 110	110 108 112 110 116 112 116 112	108 116 108 114 104 120 98 118	215:118	150:90 150:90	184:96	228 226 228 228 230 226 230 230	154 150 154 154 148 148	136:70 130:76 134:76 134:80 130:74 132:78	134 138 136 132 136 134	212 186 210 182 188 188 188 178 184 178 188 174 186 176 184 176		
Radials.....	96 90 98 90	112† 122 114 126 118 118 118 116 126 128	96 100 96 100	112 104 106 104 108 102 110 106	112 98 108 104 112 104 104 106 118 116	120 108 118 120 110 120 106 114	200:110	148:90 148:90	186:100	216 218 212 218	160 154 166 152 154 164 150 150	130:90 140:98 138:86 140:88 130:86 140:96	150 142 148 138 148 144 144 140	200 210 300 210 232 210 300 220		
Brachials.....	106 108 108 108	132 122 128 120 130 122	104 104	120 114 116 112 112 112	110 108 120 110 104 104 118 116	108 118	210:114	.....	.....	228 222 218 214	148 146 146 146	124:70 130:78	128 128 128 130	184 172		
Radials.....	98 88 94 90 90*† 86†	126 128	. .	106 104 112 102 110 114 106 106 104 110	106 104 106 102 106 102 106 102 104 110	112 106 110 104 110 110	204:116	.....	.....	200 214 200 216	156 150 150 156	134*† 142	188 138 142 142	260 208		
Brachials.....	108 104 108 104 110 102 106 100	124 132 122 124 132 132	. .	... ..	114 110	116 114	218:118	.....	.....	226 224 226 224	146 146 146 146	.....	128 138 124 132 128 130			
Radials.....	96 94 90 86	... ..	... ..	... ..	... ..	... ..	198:118	.....	.....	... ..	... ..	.....	140 142			

\* All by auscultation.

† By palpation.

does not explain why the blood pressure in the soft radial was higher than that in the corresponding sclerotic brachial artery. The fact that most of the time we used the palpatory method for the radial and the auscultatory method for the brachial arteries is to be noted, but this might tend to give an even lower reading for the radial and, therefore, does not explain our results. On the first day we used auscultation for both radial and brachial arteries and still found the radial readings higher. In the patients with marked sclerosis, the auscultatory method revealed practically no sounds at any level of pressure over the radial arteries. Our suggestion for being able to feel an impulse in the radial arteries of patients 12, 13 and 14 when the pressure in the cuff over these arteries was as much as 100 mm. higher than the known blood pressure (table 5) is that we were feeling a transmitted shock which passes from the pulse above the cuff over the rigid empty vessel under the cuff and on to the examiner's finger. The more marked the sclerosis, the easier is the transmission. This possibility is further borne out by the fact that in case 14, although we could feel an impulse over the right radial artery at 300 mm., the Tycos recording apparatus did not record a pulse wave above 200 mm. This could mean only that at 300 mm. we were not dealing with an expansile pulsation, but rather with a transmitted vibratory impulse which could not be recorded on the Tycos oscillogram.

#### SUMMARY AND CONCLUSIONS

Simultaneous bilateral readings of the blood pressure in the radial arteries were made in a patient who both clinically and radiographically had a soft radial vessel on one side and a sclerotic radial vessel on the other side. Our results are in accord with evidence obtained previously in studies with excised vessels, and our observations indicate that the sclerotic arterial wall has no significant effect on the determination of blood pressure. It was also found that in this patient, as well as in three other patients with marked radial sclerosis, the radial blood pressure reading was higher than the brachial blood pressure reading.

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# CLINICAL STUDIES OF RESPIRATION

## I. PLETHYSMOGRAPHIC STUDY OF QUIET BREATHING AND OF THE INFLUENCES OF SOME ORDINARY ACTIVITIES ON THE EXPIRATORY POSITION OF THE CHEST IN MAN

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Alterations in the respiratory movements may consist in a change in the rate, rhythm or amplitude of the respirations or in the expiratory position of the chest, or in several of these combined. The factors that influence the rate, rhythm and amplitude of the respirations have been carefully studied by numerous investigators, and the subject has been thoroughly reviewed by Haldane,<sup>1</sup> Gesell<sup>2</sup> and Means,<sup>3</sup> but the factors that alter the expiratory position of the chest have received less study.

Changes in the expiratory position of the chest were encountered during a study of oxygen debt after muscular work in patients with hyperthyroidism. The consumption of oxygen as determined by the closed circuit method increased rapidly during work, whereas immediately after work it decreased to or below the previous basal level, so that a lack of oxygen was not demonstrable. The respiratory quotient declined during work to 0.7 or below, and increased after work to 1 or above. These observations could not be explained entirely by the change in the caloric value of oxygen or by a decreased excretion of carbon dioxide during work, but could be explained by a storage of oxygen in the body during work, with some utilization of this stored oxygen after work. Since Bohr<sup>4</sup> and Rubow<sup>5</sup> showed that the vital

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1. Haldane, J. S.: *Respiration*, New Haven, Conn., Yale University Press, 1927.

2. Gesell, R.: *The Chemical Regulation of Respiration*, *Physiol. Rev.* **5**:551, 1925.

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4. Bohr, C.: *The Functional Variations in the Middle Position and Vital Capacity of the Lung: Normal and Pathological Emphysema*, *Deutsches Arch. f. klin. Med.* **88**:385, 1906-1907.

5. Rubow, V.: *Study of the Respiration of Heart Disease: A Contribution to the Study of the Pathology of the Lesser Circulation*, *Deutsches Arch. f. klin. Med.* **92**:255, 1907.



middle position of the chest (*Mittellage*) increased after work, a sphygmomanometer cuff attached to a tambour was fastened around the chest to determine the relative volumes of the chest before, during and after work. This study showed an increase in the volume of the chest during work and a decrease after work.

Since changes in the volume of air in the lungs at the end of expiration may alter the effective ventilation of the lungs, it is desirable to study the factors that cause this alteration in the respiratory movements.

Davy<sup>6</sup> was the first to determine the residual air of the lungs in the living, and Hutchinson,<sup>7</sup> by the use of the spirometer, was the first to study the vital capacity. Bohr,<sup>4</sup> Rubow,<sup>5</sup> Siebeck<sup>8</sup> and Bittorf and Forschback<sup>9</sup> emphasized the vital middle position of the chest, while Peabody and Wentworth<sup>10</sup> showed the relation of the vital capacity to dyspnea. Lundsgaard and Van Slyke<sup>11</sup> improved the technic for the determination of the residual air of the lung and studied the different components of the external respiration, but these methods do not give a continuous record of the relative volumes of the chest, and therefore sudden changes in the volume of the chest cannot be determined.

The use of a body plethysmograph was suggested by Bohr<sup>4</sup> but was abandoned without a trial because he thought the gas in the gastro-enteric tract might interfere. Binger and Davis<sup>12</sup> used a body plethysmograph to study the respirations of patients with pneumonia, but the entire body, with the exception of the head and neck, was enclosed in the apparatus, and it was therefore not suitable for this study.

#### METHOD

A body plethysmograph was constructed by means of a rubber bag covered with sateen. The bag was made from large, thin sheets of pure gum rubber and designed to cover the anterior and lateral surfaces of the body from the neck to the pubis and to project onto the shoulders. Its shape is shown in figure 1.

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The projections onto the shoulders were fastened by straps, which were crossed in the back; these, like the strap around the pelvis, were fastened snugly about the body. The remaining straps were tightened just enough so that when the subject was in the supine position, the lateral margins of the rubber bag were brought into line with the junction of the subject's back and the bed. The bag was connected to a spirometer by a large hose, and the movements of the spirometer were recorded on kymograph paper ruled in millimeters. After the

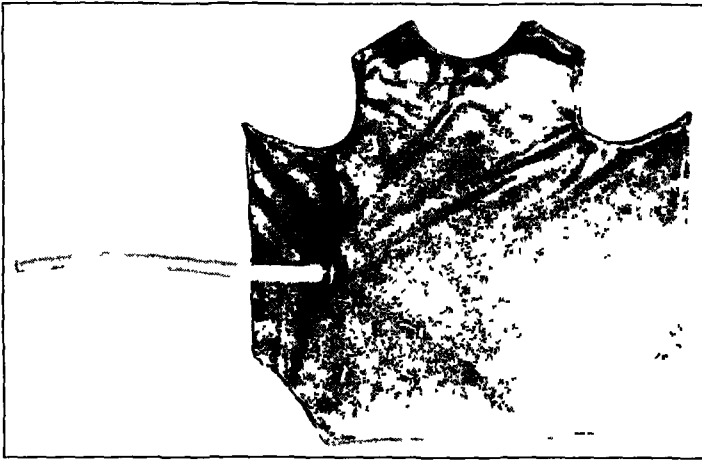


Fig. 1.—The shape of the body plethysmograph when deflated.

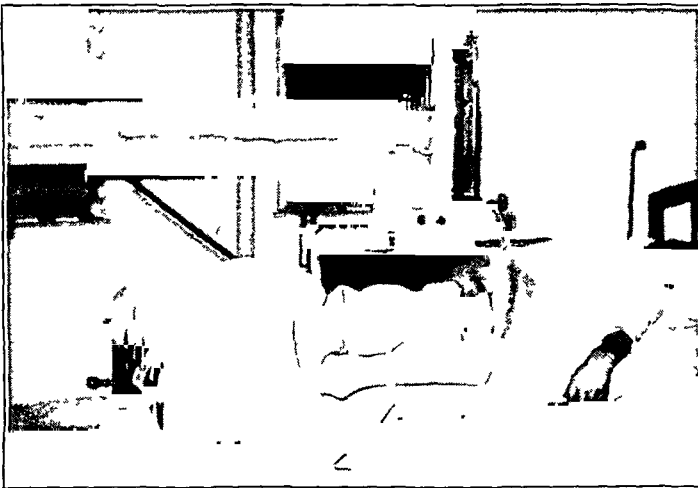


Fig. 2.—The plethysmograph applied to a subject.

bag was fastened to the body and connected to the spirometer, it was tightly filled with air to eradicate any wrinkles, and the pressure in the apparatus was adjusted by the addition of a weight of 300 Gm. to the top of the spirometer bell. The apparatus is shown applied to a subject in figure 2.

The design of the plethysmograph was later changed in an attempt to make the outer wall more rigid. A wooden cradle was constructed, which extended from the axillae to the pubis, at from 8 to 10 inches (20 to 25 cm.) above the body. The cradle was lined with sateen, which projected forward and was fastened

around the neck of the subject. The caudad end was fastened snugly around the pelvis. The hose connected to the rubber bag was fastened to the top of the cradle.

The accuracy of the apparatus was determined on forty subjects by simultaneous records with a spirometer attached to the mouth. Both spirometers had a volumetric equivalent of 20.73 cc. per millimeter change in the height of the spirometer bell. The movement of the bell of the plethysmographic spirometer varied with different subjects and with different applications of the apparatus to the same subject. When the change in volume was large, it compared favorably with the spirometer attached to the mouth; the movement of 1 mm. on the plethysmographic record was equivalent to an average change of 23.5 cc. of air in the lungs, the range being from 22 to 26 cc. With the smaller changes in volume which were encountered in quiet breathing, the volumetric range was from 22 to 42 cc. with different persons and with different applications of the apparatus to the same person. However, when the volumetric value of a change of 1 mm. on the plethysmographic record was determined two or more times during the same application of the plethysmographic bag, it never varied over 5 cc., or 16.6 per cent. A few subjects were encountered who persistently showed only small changes in the movement of the plethysmographic record. The reason for this is not known; most of these subjects, however, were obese and had shallow respirations.

False results, particularly as related to the expiratory position of the chest, may be obtained by any external pressure on the rubber bag, e.g., through adduction of the arm or flexion of the neck.

Although the volumetric values obtained by this method vary with the depth of respiration, with different persons and with different applications of the bag in the same person it still permits the continuous study of the relative volumes of the lungs with a certain degree of accuracy when standardized with each application of the apparatus.

#### RESULTS AND COMMENT

*Expiratory Position of the Chest During Quiet Breathing.*—During breathing in repose, in a majority of the subjects the expiratory position of the chest was more constant than the inspiratory position. This is in accord with the findings of Hendry, Carpenter and Emmes.<sup>13</sup> Figure 3, graph A, shows the most common type of quiet breathing. The down stroke is expiration, and the graph is read from right to left. The expiratory position is shown to be almost constant. Graph B shows a fluctuating expiratory position of the chest, which was encountered in a few apparently normal persons and which has been called undulatory breathing.

It was shown by Musso<sup>14</sup> that the respirations of normal adults in repose were fairly regular in rhythm, amplitude and "muscular tone," but that the depth of inspirations may vary in a rhythmical way and that this is more common in young and elderly persons. Conner and

13. Hendry, M. F.; Carpenter, T. M., and Emmes, L. E.: Gaseous Exchange with Unpractised Subjects and Two Respiratory Apparatus Employing Three Breathing Appliances, Boston M. & S. J. **181**:285 (Sept. 4), 334 (Sept. 11) and 368 (Sept. 18) 1919.

14. Musso: La respiration periodique et la respiration superflue ou de luxe, Arch. ital. de biol. **7**:48, 1866; quoted by Conner and Stillman.<sup>15</sup>

Stillman<sup>15</sup> observed undulatory breathing in some normal persons and a more marked disturbance of the same type in patients with meningitis. Changes in the expiratory position of the chest during undulatory breathing have also been shown by Neilson and Roth.<sup>16</sup> Periodic breathing and periodic irregularities in the respirations of some subjects in repose were observed by Reed and Kleitman,<sup>17</sup> but the irregularity usually disappeared during sound sleep. Conner and Stillman<sup>15</sup> stated that in elderly persons undulatory breathing is more pronounced during sleep. The subjects of our study were from 20 to 50 years of age, and only a few were studied during sleep. In those studied, the character of the respiration and the changes in the volume of the thorax

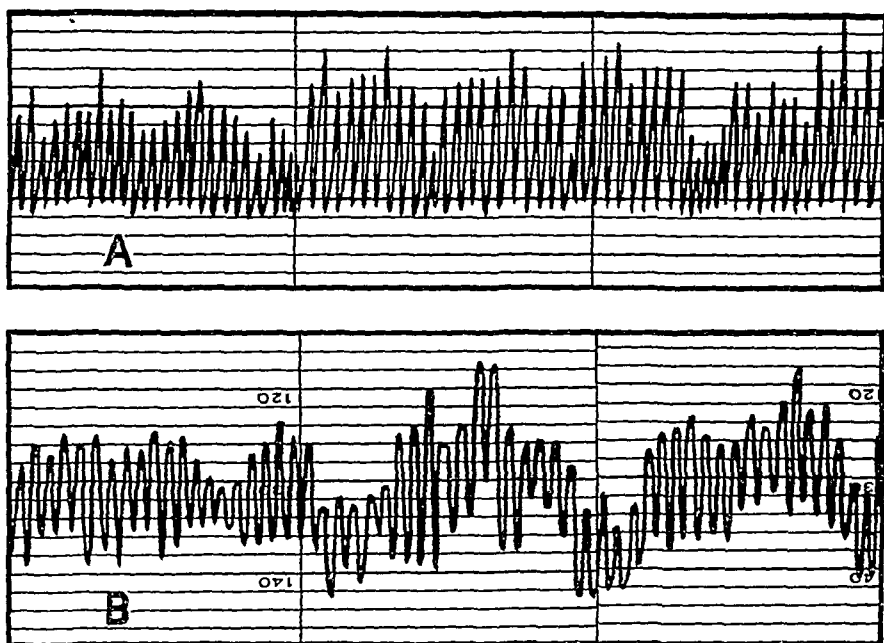


Fig. 3.—*A*, the most common type of quiet breathing; *B*, fluctuating expiratory position of the chest.

were of the same type during sleep as in the basal state, but the actual changes in volume were decreased. One subject who had fluctuations of the expiratory position in the basal state exhibited the same fluctuations during sleep, but to a lesser degree, as shown in figure 4 (graph A). The graphs are read from right to left, and the down stroke indicates expiration. This patient snored at irregular intervals; the effect of the

15. Conner, L. A., and Stillman, R. G.: A Pneumographic Study of Respiratory Irregularities in Meningitis, *Tr. A. Am. Physicians* **26**:464, 1911.

16. Neilson, J. M., and Roth, P.: Clinical Spirography, *Arch. Int. Med.* **43**:132 (Jan.) 1929.

17. Reed, C. I., and Kleitman, N.: Studies on Physiology of Sleep: IV. Effect of Sleep on Respiration, *Am. J. Physiol.* **75**:600, 1925.

snoring on the respirations is shown in graph B at 1 and 2. At the end of the apnea, at 2, the subject jumped as though startled, and then hyperpnea began. After the subject was awakened, he stated, without being questioned, that he had dreamed that some one was choking him and that he "had to get free to breathe."

*Effect of Changing the Body Position on the Expiratory Position of the Chest.*—The influence of changing the body from the horizontal to the vertical position was studied first by Panum<sup>18</sup> and later by Loven.<sup>19</sup> The results varied, and the interpretation was a disputed point between these investigators. The differences in the results may have been due to the methods employed and to the length of time

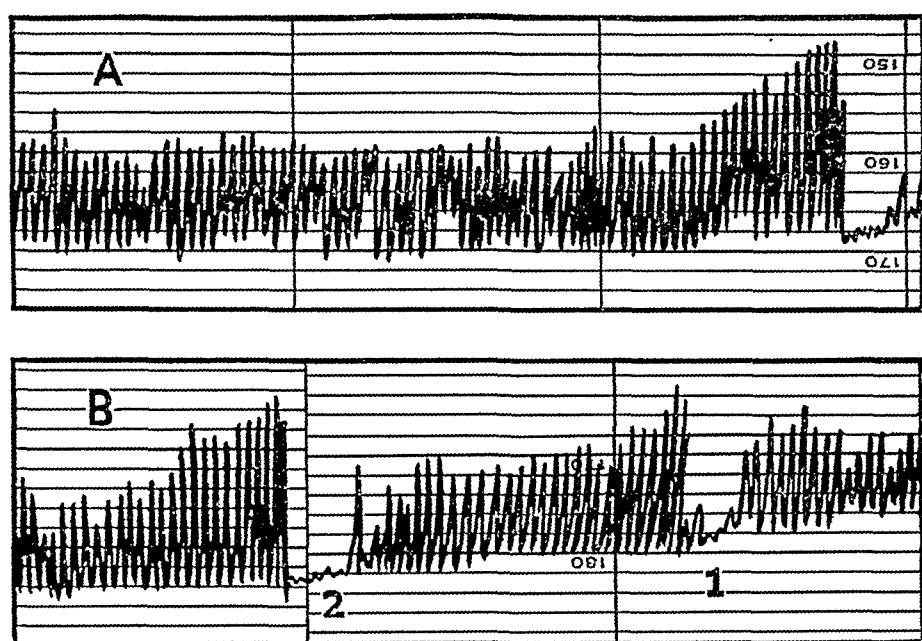


Fig. 4.—*A*, fluctuation of the expiratory position during sleep; *B*, at 1 and 2, effect of snoring on respirations.

necessary for the effect to become manifest after the change in body position. Bohr<sup>4</sup> found that the vital middle position was increased when the body was changed from the horizontal to the vertical position. He obtained this increase when the body was changed from the horizontal to the sitting position, but there was no further increase when changed from the sitting to the standing position. The time necessary for the appearance of this increase varied, requiring several minutes in some instances.

Since the plethysmographic method gives a continuous record of the changes in the relative volume of the chest, the influence of changing the body position was studied to learn if this method would record

18. Panum, P. L.: Arch. f. d. ges. Physiol. 1:125, 1868; quoted by Bohr.<sup>4</sup>

19. Loven, C.: Nord. med. ark. 4:1, 1872; quoted by Bohr.<sup>4</sup>

the changes in volume due to changes of the body position, the length of time necessary for the effect to be obtained and, lastly, the accuracy of the plethysmographic method when used to measure this effect.

A record of the quiet breathing was obtained with the subject in the supine position on a tilting table. The body position was altered by tilting the table to the vertical or horizontal positions.

Bohr<sup>4</sup> and others had shown that muscular exertion increases the middle position, but in our study the only muscular exertion performed was that necessary for the support of the body weight in the vertical position.

The increase of the expiratory position of the chest due to the change of the body from the horizontal to the vertical position and the decrease of the expiratory position of the chest when the body was returned to the horizontal position are shown in figure 5, graphs A and B. The graphs are read from right to left; the down stroke indicates expiration. Graph A is a plethysmographic record taken simultaneously with the spiographic record, graph B. At 1, the change to the vertical position was begun; at 2, the vertical position was assumed; at 3, the change to the horizontal position was begun, and at 4, the horizontal position was assumed.

The changes in the volume of the thorax when the body position was changed were almost instantaneous when the subject was relaxed. In all three of the subjects studied, however, the volume changes that occurred with the change of body position varied until the subject had become accustomed to the procedure. In some instances, the volume decreased when the body was changed to the vertical position, and there was an increase in volume when it was returned to the horizontal position; in some instances there was no apparent change in the volume even after eight minutes. The change in volume apparently depends on the balance in tone of the muscles of the thorax, abdomen and diaphragm. Undoubtedly, there was not complete relaxation when these varied results were obtained, because the subjects were not accustomed to the sensations derived from the procedure. When the body was changed from the horizontal to the vertical position, there was in the abdomen a sensation of "sinking" similar to that obtained when one goes up in a rapidly moving elevator, and when the body was changed back to the horizontal position there was a "rising" sensation in the abdomen such as is encountered when one goes down in a rapidly moving elevator. A compensatory change in the tone of the muscles undoubtedly occurred, as illustrated by figure 5, graph C. Graph C is a plethysmographic record of the respirations before the subject became accustomed to the procedure. Inflation occurred when the body was changed from the horizontal to the vertical position. This procedure was begun at 1, and was completed at 2. Deflation occurred almost

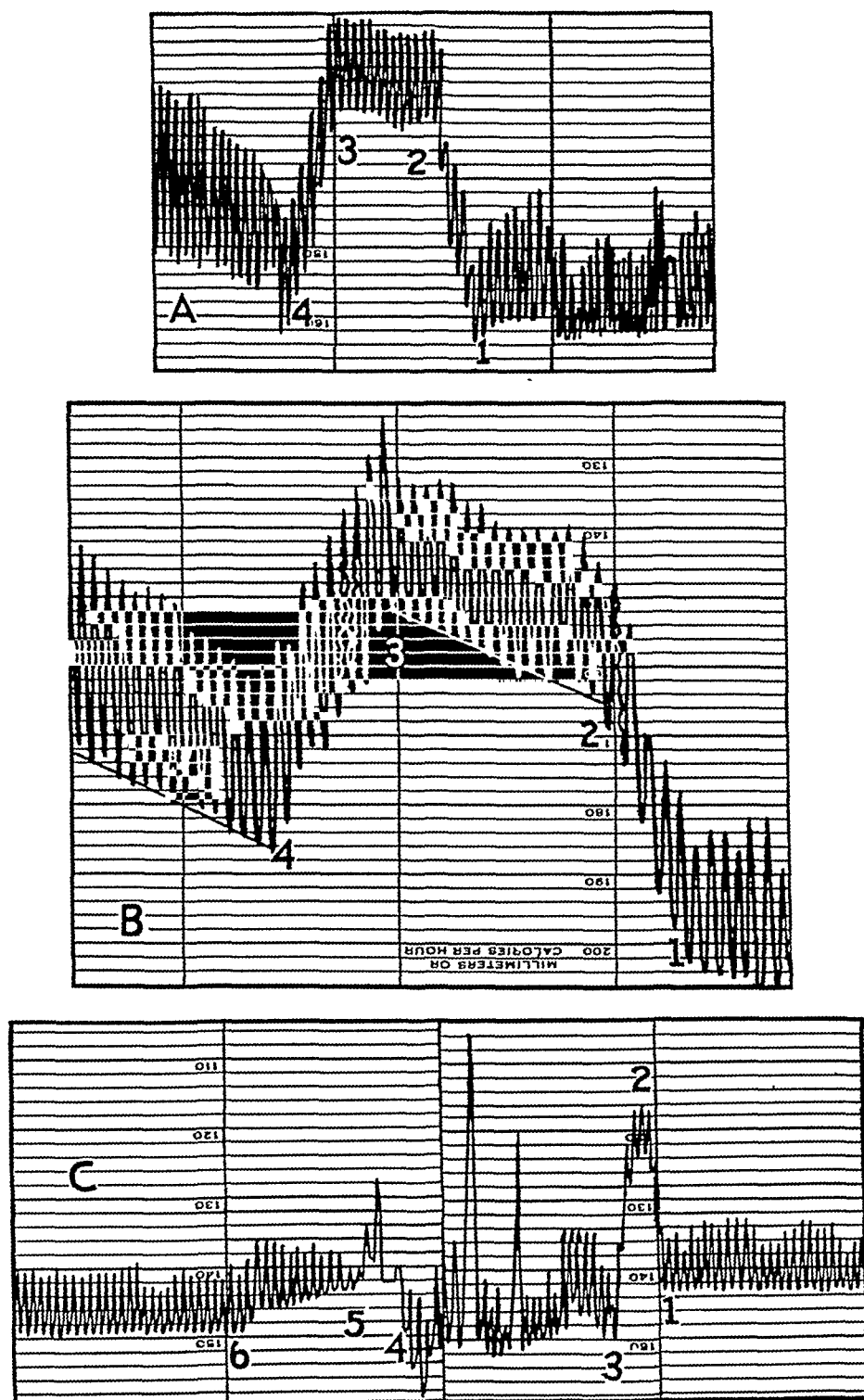


Fig. 5.—Effect of change of body position on the expiratory position of the chest: *A*, plethysmographic record; *B*, spiographic record; *C*, period of adjustment to changed position.

immediately, without further change in the position of the body, and was completed at 3. The respirations were altered in character during the time the body was in the vertical position. A slight inflation occurred when the body was returned to the horizontal position, which was begun at 4 and completed at 5. About one minute was required before the respirations became normal at 6.

This variation in tone of the diaphragm, thoracic and abdominal muscles would explain Bohr's observations of the variations in the length of time necessary for characteristic changes to occur, and also why Panum and Loven obtained varying results, since their studies were made at short intervals.

The accuracy of the plethysmographic method for determining the expiratory position of the chest due to changes in the position of the body was determined by the simultaneous spirographic and plethysmographic records, shown in figure 5, graphs A and B. The volume of the air in the chest increased 891.4 cc. by the spirographic method and 870.6 cc. by the plethysmographic method when the body was changed from the horizontal to the vertical position.

*Effect of Slight Muscular Work on the Expiratory Position of the Chest.*—Bohr<sup>4</sup> and others showed that slight muscular work will increase the middle position of the chest, but the methods employed did not give continuous records of the relative volumes of the chest; therefore it was not known when this increase occurred. Bohr<sup>4</sup> considered this increase to be a compensatory mechanism that widened the capillaries of the lung and aided the circulation, whereas Bittorf and Forschback<sup>9</sup> thought it to be a reflex phenomenon which, in some instances, was detrimental to the proper gaseous exchange.

To study the influence of muscular exertion on the expiratory position of the chest, a record of quiet breathing was obtained with the subject in the supine position. The subjects were cautioned against dorsal flexion of the spine and against forward projection of the chest wall. A measured amount of muscular work by flexion of the forearm against an ergograph was then performed.

The influence of muscular work on the expiratory position of the chest is shown in figure 6. An increase in the expiratory position is shown in graphs A, B and C, while graphs D and E show no effect during muscular work. Graph A, B and D are plethysmographic records. Graph C and E are spirographic records. Graphs B and C and graphs D and E are simultaneous records. Work was begun at 1 and was discontinued at 2.

In the two subjects who showed an increase in volume of the chest, the volume increased immediately after work was begun. With the second subject (graphs B and C), the volume decreased slightly after the initial increase and returned to its previous level immediately after



work ceased, while with the first subject (graph A) the volume continued to increase as long as work was performed and had not returned to its previous level five minutes after the work had ceased.

These observations indicate that the increase of the volume of air in the chest at the end of expiration during work may be a reflex mechanism; however, when the arm is flexed at the elbow, some of the

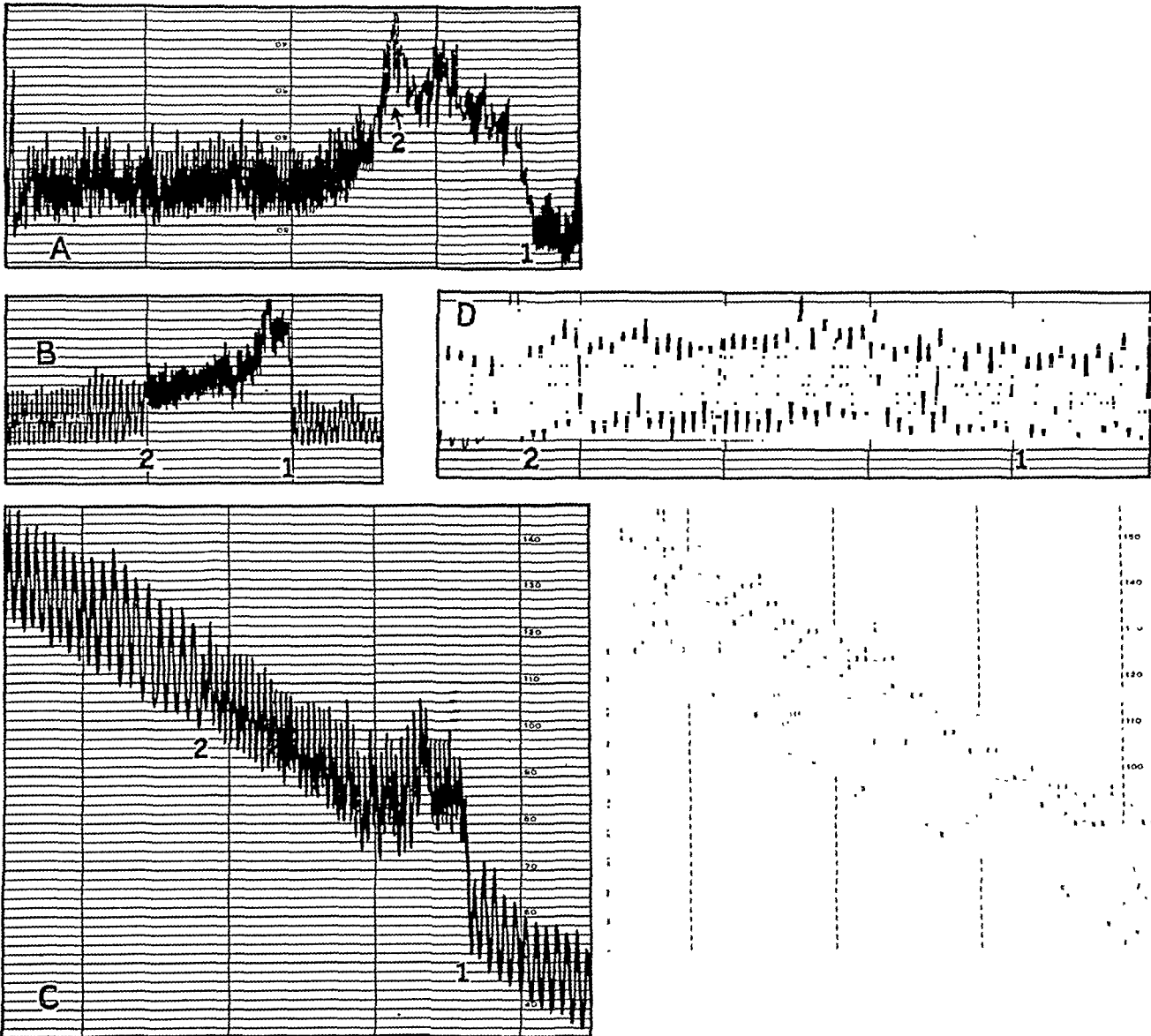


Fig. 6.—Influence of muscular work on the expiratory position of the chest.

muscles of the shoulder girdle contract, and this may have exerted an influence to change the volume of the thorax. In order to decrease or exclude this factor, the subject gripped the hand against a dynamometer, and the influence on the expiratory position was determined. There was an increase in the volume of the thorax when the hand was gripped, as shown in figure 7. This increase is not simply an inspiration, because the respiratory motions are continued during the inflation.

Graphs A and B are plethysmographic records of the respirations. The expiratory position of the chest increased when the hand was gripped at 1, and decreased after the hand was relaxed at 2.

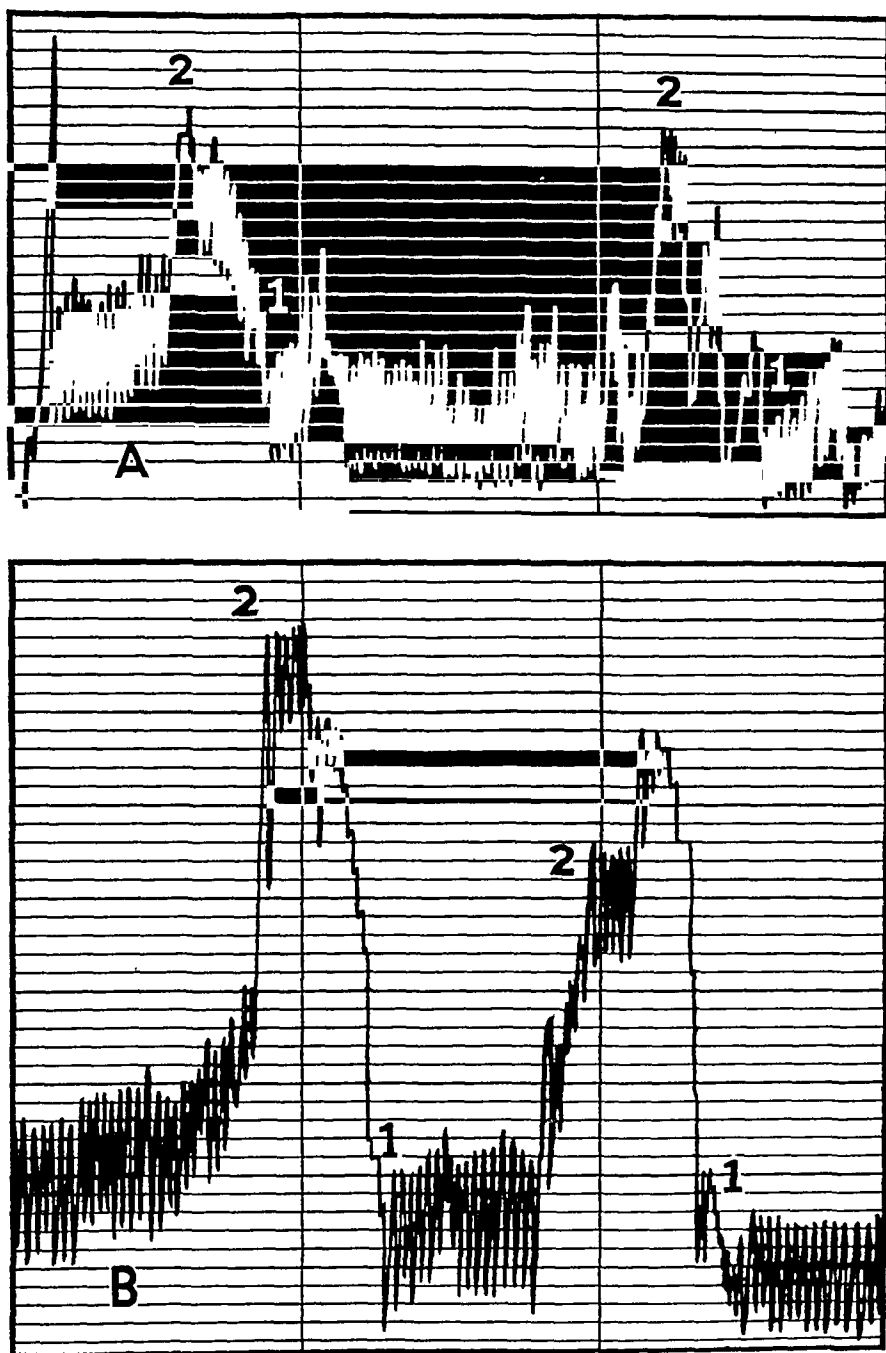


Fig. 7.—Influence exerted on the expiratory position when the subject gripped a hand against a dynamometer.

Care must be taken, however, to prevent adduction of the arm against the plethysmographic bag, or false results will be obtained.

*Influence of Short Periods of Talking and Reading on the Expiratory Position of the Chest.*—Because the use of the voice apparently alters the respirations more than any of the ordinary activities, the influence of talking and reading aloud was studied, and the results are shown in figure 8. The graphs are plethysmographic records; talking began at 1 and ceased at 2. In graph B, reading aloud began at 3 and ceased at 4. The speed of the kymograph was one half as great in graph B as in graph A.

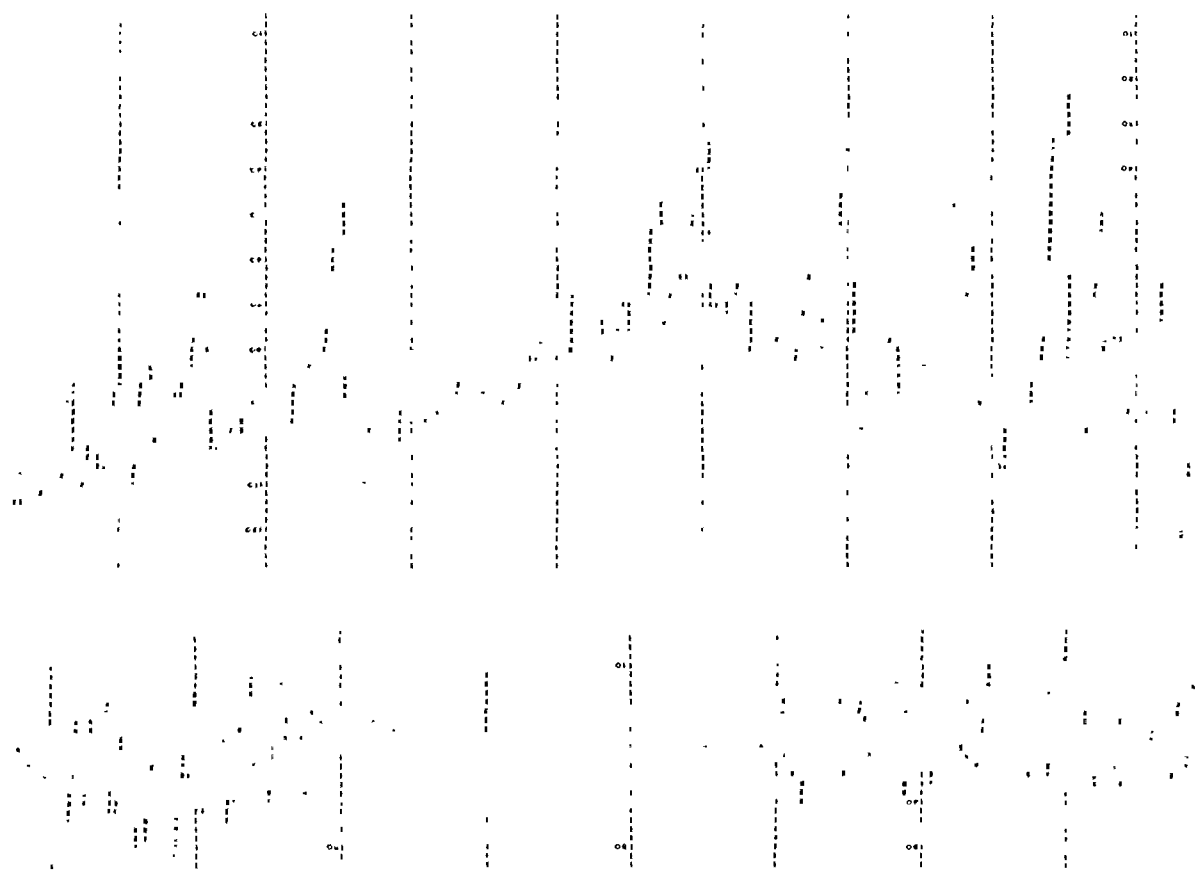


Fig. 8.—Influence of talking or reading aloud on the expiratory position.

The speech of the first subject was faltering, the sentences were short, the trend of thought was not connected, the subject appeared bashful, and the expiratory position increased markedly. The second subject was at ease, the sentences were long, the thought was connected, and the expiratory position varied. The end of expiration appeared to be controlled by the pauses in the sentence and at the end of the sentence. In graph B, following talking and reading, there was a definite decrease in the frequency and amplitude of the respirations, which indicated that an excess amount of carbon dioxide was eliminated during the periods of talking.

## SUMMARY

1. A plethysmographic method for the study of the respiratory movements in man has been described.

2. The expiratory position of the chest in repose is more constant than the inspiratory position, but the expiratory position may also fluctuate in apparently normal subjects.

3. After the subject has become accustomed to the procedure, the volume of air in the lungs at the end of expiration increases immediately when the body is changed from the horizontal to the vertical position and decreases immediately when the body is returned to the horizontal position.

4. The expiratory position of the chest may or may not increase with slight muscular work. If it increases, the time required for it to return to its previous level varies.

5. The false results obtained by the method are discussed.

6. The expiratory position of the chest and the depth of the respirations during talking and reading aloud appear to depend on the length of the sentences and phrases when the subject is at ease and when hyperventilation may occur.

# THE QUESTION OF THE PRESENCE OF A PRESSOR SUBSTANCE IN THE BLOOD IN ESSENTIAL HYPERTENSION

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The etiology of essential hypertension is still obscure. Perhaps subsequent research will disclose multiple etiologies and will demonstrate the term to be generic rather than specific. Among the numerous postulates that have been advanced to explain the genesis and maintenance of the hypertension which is pathognomonic of this disease is that of the possible presence of a pressor substance in the blood. Thus Danzer, Brody and Miles<sup>1</sup> found a rise in blood pressure after the intravenous injection of unchanged specimens of blood from patients with hypertension into atropinized cats that had been desensitized to human blood, and concluded that there is a pressor substance in the blood in hypertension. Using the same technic, Danzer<sup>2</sup> later reported similar results from a majority, but not from all, of the tested specimens of blood of patients with hypertension. On the other hand, Stewart<sup>3</sup> obtained no pressor effects from the intravenous injection of serums from patients with hypertension into dogs, and Bröking and Trendelenburg<sup>4</sup> found no increase in the vasoconstricting properties of hypertensive blood serums, as compared with normal serums, by means of perfusion experiments on frogs. Curtis, Moncrieff and Wright,<sup>5</sup> moreover, found no definite pressor effects from the intravenous injection of specimens of hypertensive blood into atropinized cats that were desensitized to human blood. Likewise, Hülse<sup>6</sup> was unable to obtain a rise in the blood pressures of

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1. Danzer, C. S.; Brody, J. G., and Miles, A. L.: *Proc. Soc. Exper. Biol. & Med.* **23**:454, 1926.

2. Danzer, C. S.: *Am. J. Physiol.* **81**:472, 1927.

3. Stewart, G. N.: *J. Exper. Med.* **14**:377, 1911.

4. Bröking, E., and Trendelenburg, P.: *Deutsches Arch. f. klin. Med.* **103**:168, 1911.

5. Curtis, F. R.; Moncrieff, A. A., and Wright, S.: *J. Path. & Bact.* **30**:55, 1927.

6. Hülse, W.: *Arch. f. exper. Path. u. Pharmakol.* **146**:282, 1929.

dogs by injecting specimens of hypertensive blood into the carotid or vertebral arteries. Furthermore, he found that the intrathecal injection of serums from patients with essential hypertension produced no increase in the blood pressures of cats.

In view of the conflicting nature of the evidence thus far adduced, we decided to study the problem by employing the more direct technic of observing the action of hypertensive and normal blood serums on the tone of arterial rings. This procedure offered an advantage over methods which employ the whole animal in that the latter, because of regulatory vasomotor mechanisms operating in the intact organism, may fail to demonstrate the pressor substance, even if it is present. However, our method offers the possibility of detecting only a circulating substance affecting the peripheral vascular tree and not one possessing central action.

As is well known, coincident with the clotting of blood, epinephrine-like substances arise in the serum.<sup>7</sup> We therefore looked for possible significant quantitative differences between the tone-augmenting properties of hypertensive serums and normal serums for arterial rings.

#### PROCEDURE

The apparatus employed was essentially that used by Meyer<sup>8</sup> in his study of the physiology and pharmacology of arterial segments and by Cow,<sup>9</sup> Barbour<sup>10</sup> and Voegtlin and Macht<sup>11</sup> in their investigations of the action of drugs on arterial segments. Rings about 4 mm. in diameter and 3 mm. in width, obtained from the tertiary division of the superior mesenteric artery of freshly slaughtered beeves, were placed in a glass chamber filled with Locke's solution at 37.5 C. The superior mesenteric branch was selected because it is known to contain relatively more smooth muscle and less elastic tissue than the carotid or the vertebral arteries, and hence was believed to be structurally more analogous to the arterioles. Oxygen was bubbled through the fluid medium bathing the arterial segment. One side of the ring was attached to the bottom of the chamber, and the other was connected to the short arm of a lever delicately balanced on a knife-like edge. The lever magnified changes in the tone of the arterial rings twenty-three times. The bottom of the chamber was drawn out and connected with rubber tubing so that the fluid in the chamber could be changed at will. The chamber was immersed in a water-jacket which maintained the temperature at a constant level.

When first set up, the arterial segment was in a state of considerable tonus, which was partially overcome by a load of 2 Gm. attached to the long arm of the lever at the same distance from the fulcrum as the attachment of the artery on the short arm. The process of relaxing the arterial ring usually took about one hour. At the end of this period, the diameter of the segment was from 6 to 8 mm. After

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7. O'Connor, J. M.: *Arch. f. exper. Path. u. Pharmacol.* **67**:195, 1912.

8. Meyer, O. B.: *Ztschr. f. Biol.* **43**:352, 1906.

9. Cow, D.: *J. Physiol.* **42**:125, 1911.

10. Barbour, H. G.: *J. Exper Med.* **15**:404, 1912.

11. Voegtlin, C., and Macht, D. I.: *J. Pharmacol. & Exper. Therap.* **5**:77, 1913.

the elasticity of the artery had reached an equilibrium, the preparation was ready for testing, the 2 Gm. weight being used as a lifting, as well as a stretching, load.

Blood serums from thirty patients with essential hypertension and from fifteen with normal blood pressures were studied. The patients were equally divided between the two sexes. In twenty of those with hypertension, symptoms were manifested that occur relatively late in the course of the disease. Each member of this group had experienced one attack of cardiac decompensation and was receiving maintenance doses of digitalis at the time when the specimen of blood was drawn. In the remaining ten patients with hypertension the condition was in a comparatively early stage. Five of these patients were free from symptoms so far as hypertension was concerned. The other five showed a mild degree of cardiac insufficiency which came under class 1 of the nomenclature for functional capacity approved by the American Heart Association.<sup>12</sup> The blood pressures of the entire hypertensive group ranged from 160 systolic and 94 diastolic to 300 systolic and 150 diastolic, with an average of 194 systolic and 115 diastolic. The results of urinalyses and of studies of the blood chemistry in all of the cases of hypertension were uniformly normal. The results of phenolsulphonphthalein tests on the group with late hypertension and of urine concentration tests (Mosenthal) on ten of the patients in this group were normal. No other studies of renal function were made. Retinal and peripheral arteriosclerotic changes were absent or were slight. The fifteen patients with normal blood pressures were the subjects of a miscellany of diseases unrelated to the cardiovascular system. In general, these patients belonged to the same age group as the hypertensive patients.

Fifteen separate experiments were made, arterial segments from a corresponding number of beeves being used. One normal and two hypertensive serums were employed for each experiment. After a kymographic record of the tone of the arterial ring in Locke's solution had been obtained, Locke's solution was replaced by one of the serums. The tone of the ring promptly increased. After an interval of twenty minutes, the serum was removed and Locke's solution was again added. The change back to Locke's solution resulted in a return of the arterial ring to its original tonus. Subsequently, the same procedure was used for the other two serums. In the different experiments the order of adding the hypertensive and normal serums was varied. At the conclusion of each experiment, the first serum tested was again added to the bath in order to demonstrate that there had been no appreciable change in the motor activity of the arterial ring or in the tone-augmenting properties of the serum for the arterial segment. This alternate contraction and relaxation of the arterial ring on the addition of serum and then of Locke's solution is similar to that described by Friedberger<sup>13</sup> for his mammalian perfusion experiments with serums and Ringer's solution.

## RESULTS

When the arterial rings were partially relaxed, one third of them showed in Locke's solution the spontaneous tonal changes illustrated in chart 1. The rhythmic oscillations varied somewhat in rate in different experiments, but in general averaged about one every two minutes.

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12. New York Tuberculosis and Health Association, Criteria for the Classification and Diagnosis of Heart Disease, New York, J. J. Little & Ives Company, 1929. p. 11.

13. Friedberger, E.: *Klin. Wchnschr.* 6:1047, 1927.

When Locke's solution was replaced by serum, the arterial segment, whether previously active or not, showed a prompt and sustained increase in tone, as illustrated in chart 2. When the serum was drained off and Locke's solution was again added, the arterial segment gradually returned to its original tonus (chart 2). This occurred in from ten to forty minutes. In almost every instance, when the serum

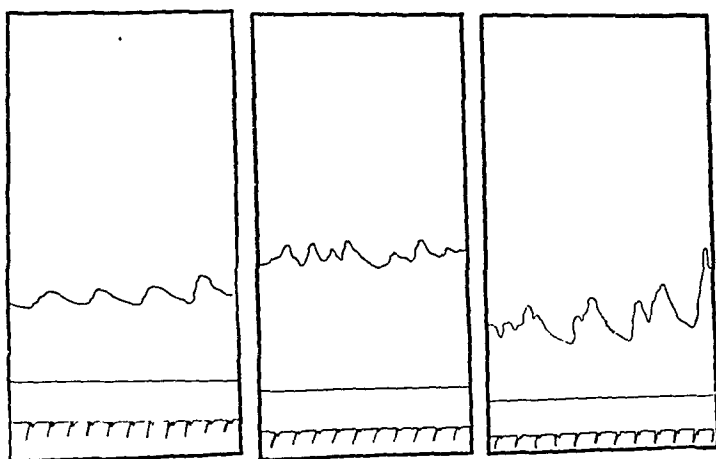


Chart 1.—Spontaneous tonus changes in three different beef arterial rings immersed in Locke's solution at 37.5 C. Intervals of one minute are recorded at the bottom.

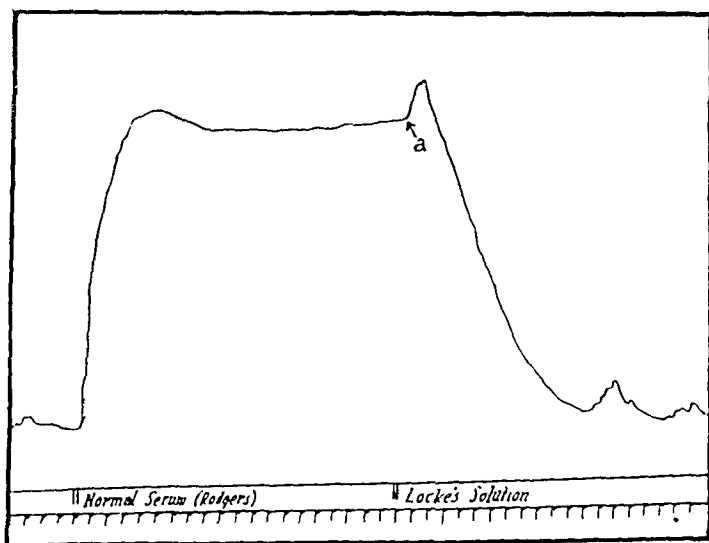


Chart 2.—Typical prompt, sustained increase in tone of an arterial segment on the addition of normal serum, followed by a somewhat more gradual relaxation of the segment on replacement of the serum by Locke's solution. The transient augmentation in tonus labeled *a* was almost invariably observed when the serum was replaced by Locke's solution. The artery shows spontaneous variations in tonus. Intervals of one minute are recorded at the bottom.

was replaced by Locke's solution, the relaxation of the arterial ring was preceded by the transient augmentation in tone labeled *a* in chart 2.



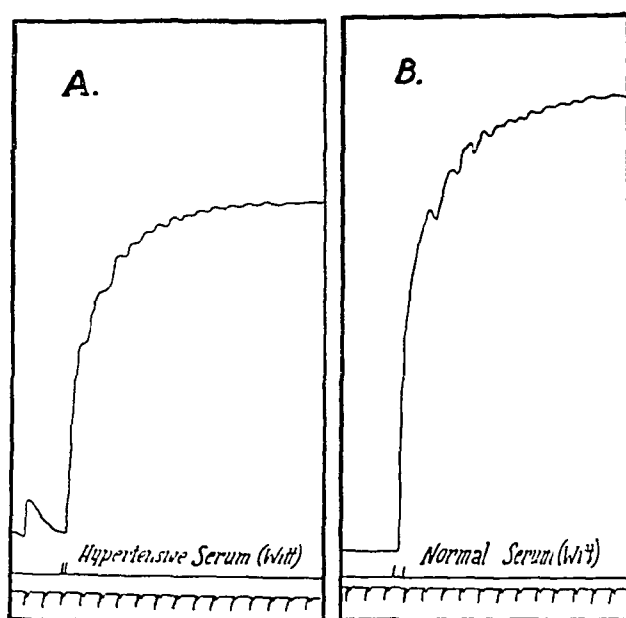


Chart 3.—Rhythmic changes in the tone of two arterial segments during the latter part of the increase in tone following the addition of serum. Segment *A* showed spontaneous motor activity. Segment *B* did not. A hypertensive serum was added to *A*. A normal serum was added to *B*.

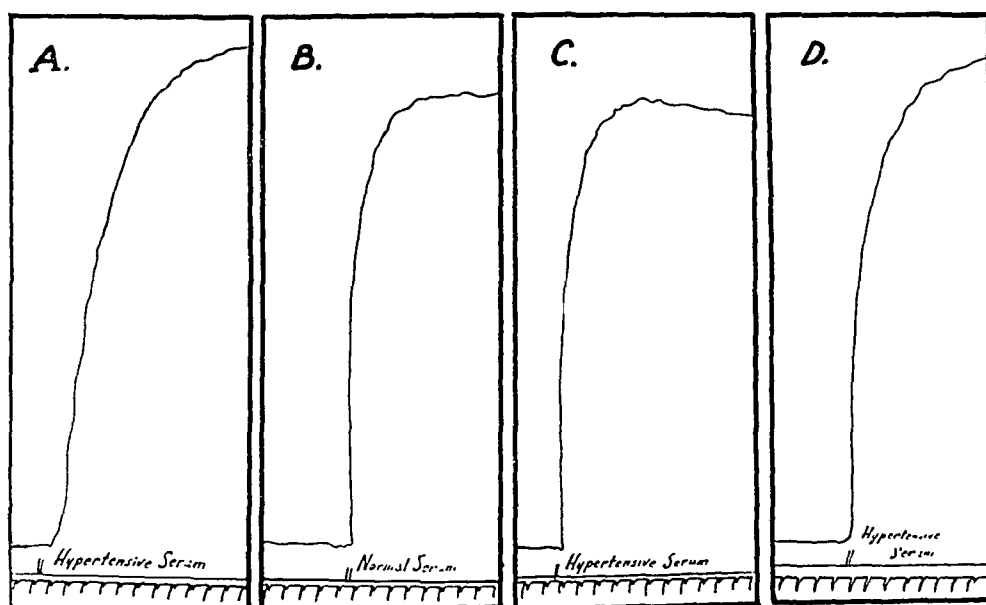


Chart 4.—Increases in the tone of an arterial segment produced successively (*A*) by a hypertensive serum from B. R. with a blood pressure of 224 systolic and 114 diastolic; (*B*) by a normal serum from G. K. with a blood pressure of 118 systolic and 80 diastolic, and (*C*) by a hypertensive serum from S. C. with a blood pressure of 282 systolic and 102 diastolic. *D* shows the increase in tone produced by a second addition of the first hypertensive serum from B. R. at the end of the experiment.

One third of the arterial rings showed a peculiar series of small rhythmic contractions and relaxations during the latter part of the increase in tonus following the addition of serum to the glass chamber. These rhythmic changes are illustrated in chart 3. They occurred at the rate of about three every two minutes and were observed in

*Increases in the Tone of Beef Arterial Rings Produced by Serums from Patients with Essential Hypertension and Serums from Patients with Normal Blood Pressures*

Experiment	Serums from Patients with Late Essential Hypertension		Serums from Patients with Normal Blood Pressures	
	Blood Pressure Readings, Systolic/Diastolic	Increases in the Tone of the Arterial Rings as Measured by the Rise of the Writing-Point of the Lever, Cm.	Blood Pressure Readings, Systolic/Diastolic	Increases in the Tone of the Arterial Rings as Measured by the Rise of the Writing-Point of the Lever, Cm.
1	210/120 200/110	8.3 8.2	124/82	7.1
2	160/ 94 170/ 90	9.4 11.5	124/80	10.4
3	170/120 198/120	11.9 12.0	134/84	11.5
4	300/150 200/124	7.4 5.1	115/90	6.7
5	220/130 170/100	4.1 5.0	120/70	5.5
6	205/130 188/110	7.7 8.2	100/70	11.8
7	220/150 160/100	8.7 8.1	100/60	11.6
8	200/100 175/140	6.3 9.9	120/80	8.0
9	182/128 164/ 96	12.3 10.0	115/60	11.5
10	160/120 180/100	4.8 6.3	100/60	8.4
Average	191/117	8.3	115/74	9.3
Serums from Patients with Early Essential Hypertension				
11	170/110 200/120	7.8 9.5	120/80	6.9
12	224/114 282/102	12.4 11.1	118/80	11.2
13	170/100 200/120	14.0 12.5	120/80	13.8
14	200/110 165/120	7.5 8.6	120/80	8.2
15	200/100 190/120	5.0 3.4	124/80	4.6
Average	200/112	9.2	120/80	8.9
Grand average	194/115	8.6	117/76	9.1

arterial rings which did not show the spontaneous rhythmic activity in Locke's solution previously mentioned, as well as in those which were spontaneously active.

Chart 4 illustrates a typical experiment with two hypertensive blood serums and a normal serum. The hypertensive serum from B. R., a white woman, aged 53, with a blood pressure of 224 systolic and 114

diastolic and a condition diagnosed as hypertensive disease of the heart and myocardial insufficiency, the latter too mild to necessitate digitalis medication, caused a rise of 12.4 cm. in the writing-point of the lever attached to the arterial segment. The normal serum from G. K., a white man, 41 years of age, with a blood pressure of 118 systolic and 80 diastolic and a condition diagnosed as gastric ulcer, resulted in a rise of 11.2 cm. The hypertensive serum from S. C., a Negro man, 49 years of age, with a blood pressure of 282 systolic and 102 diastolic and a condition diagnosed as hypertensive disease of the heart and early myocardial insufficiency, caused an elevation of 11.1 cm. A second addition of the first hypertensive serum from B. R. at the end of the experiment resulted in a rise of 12 cm., thus demonstrating that there had been no appreciable change in the motor activity of the arterial segment or in the tone-augmenting properties of the serum during the course of the experiment. These differences between the constricting properties of the three serums for the arterial ring were not significant.

The results obtained in the rest of the series of fifteen experiments were similar and are summarized in the accompanying table. As seen from this table, the average rise of the writing-point was 8.3 cm. for serums from the patients with late hypertension; 9.2 cm. for the serums from patients with early hypertension; 8.6 cm. for all of the serums from patients with hypertension, and 9.1 cm. for all of the serums from patients with normal blood pressure. In other words, there was no evidence of the presence of larger amounts of vasoconstricting or pressor substances in the hypertensive serums as opposed to the normal serums. Nor was there any correlation between the increase in the arterial tone produced by the various serums and the blood pressures of the patients from whom the serums were obtained.

#### COMMENT

The spontaneous rhythmic tonal changes in Locke's solution previously described for five of the fifteen arterial rings suggest that arterial musculature, under certain conditions at least, manifests an inherent rhythmic motor activity quite independent of extrinsic nervous connections.

Adler,<sup>14</sup> Hess<sup>15</sup> and others observed rhythmic variations in arterial tonus in vivo, and Meyer,<sup>16</sup> Günther<sup>17</sup> and Rigoni<sup>18</sup> noted the appear-

14. Adler, I.: *J. Pharmacol. & Exper. Therap.* **8**:297, 1916.

15. Hess, W. R.: *Arch. f. d. ges. Physiol.* **173**:243, 1919.

16. Meyer, O. B.: *München. med. Wchnschr.* **57**:1571, 1910.

17. Günther, G.: *Ztschr. f. Biol.* **65**:401, 1915.

18. Rigoni, M.: *Boll. d. Soc. ital. di biol. sper.* **3**:565, 1928; abstr., *Ber. ü. d. ges. Physiol. u. exper. Pharmakol.* **48**:584, 1929.

ance of rhythmic changes in the tone of arterial segments immersed in serum for approximately an hour. Janeway, Richardson and Park<sup>19</sup> observed rhythmic variations in the tone of arterial strips in Ringer-Locke solution entirely analogous to the changes described by us.

For the transient increase in tone which followed the replacement of serum by Locke's solution, we have no satisfactory explanation to offer.

Cow<sup>9</sup> has already described the rhythmic tonal changes occurring during the latter part of the increase in arterial tonus after the addition of serum to the chamber containing the arterial segment. He suggested that they may be responsible for the Traube-Hering blood pressure waves in the intact animal, but this seems to us unlikely.

The absence of significant quantitative differences in the tone-augmenting properties of the hypertensive and the normal serums for arterial rings speaks against the presence in the blood of patients with essential hypertension of a pressor substance acting to increase the tone of the peripheral vascular bed. The findings constitute merely a small link in the chain of negative evidence relative to this question. This becomes more apparent when certain limitations inherent in the method are considered. Thus the process of clotting may have altered or destroyed the pressor substance originally present. The effects of serums on arterial rings in vitro are not necessarily analogous to the effects on arterioles in vivo. The use of human serums and of beef arterial rings introduced an unknown factor of species difference. Furthermore, the effect of the possible pressor substance may have been overshadowed by the effect of the epinephrine-like bodies in the serum, unless the former was present in at least moderate quantities or acted to sensitize the vasoconstrictor nerve-endings to the latter. However, when considered jointly with the negative findings of Curtis, Moncrieff and Wright, Stewart, Bröking and Trendelenburg and Hülse, the results presented suggest that the pathogenesis of essential hypertension must be sought for elsewhere.

#### CONCLUSIONS

1. The action of thirty blood serums from patients with essential hypertension and of fifteen serums from patients with normal blood pressures on the tone of arterial segments from the mesenteric arteries of beeves was studied.

2. No significant differences were found in the vasoconstricting properties of the hypertensive and of the normal serums.

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19. Janeway, T. C.; Richardson, H. B., and Park, E. A.: Experiments on the Vasoconstrictor Action of Blood Serum, *Arch. Int. Med.* **21**:565 (May) 1918.

3. The results suggest that there is no peripherally acting pressor substance in the blood of patients with essential hypertension.

4. Some evidence was obtained for the residence of a spontaneous, rhythmic motor activity in arterial musculature deprived of its extrinsic innervation.

Dr. John Walker Moore rendered patients at the Louisville City Hospital and the outpatient department available for this study.

# TREATMENT OF NEUROSYPHILIS

REVIEW OF RESULTS IN SIX HUNDRED AND EIGHTY PATIENTS

H. HANFORD HOPKINS, M.D.

BALTIMORE

Since the analyses of the results of treatment of patients with neurosyphilis by Stokes and Osborne (1921),<sup>1</sup> Fordyce (1924),<sup>2</sup> Stokes and Shaffer (1924)<sup>3</sup> and Moore (1927),<sup>4</sup> no similar studies dealing with large numbers of cases have been published. The accumulation of further experience with modern methods of treatment permits a report of the results obtained among 1,200 patients treated in the syphilis division of the medical clinic of the Johns Hopkins Hospital.

The clinical material on which the study is based is presented in table 1. All patients are included who on admission presented evidence of neurosyphilis or in whom it subsequently developed. The whole group of 1,199 patients was used for an estimation of the effect of previous inadequate treatment on the period of incubation of clinical neurosyphilis; the results of this study have been published.<sup>5</sup>

Following the practice of Head and Fearnside,<sup>6</sup> Stokes and Shaffer<sup>3</sup> and Moore,<sup>4</sup> the cases were divided according to their clinical manifestations into the following groups:

1. Early neurosyphilis. The manifestations are in most instances based on purely meningeal changes, and they almost always occur within the first two years of the disease. The group includes acute syphilitic meningitis, neurorecurrence and early asymptomatic neurosyphilis.<sup>7</sup>

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From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital.

This investigation was supported by a grant from the Committee on Research in Syphilis, Inc.

1. Stokes, J. H., and Osborne, E. D.: Relative Effectiveness of Various Forms of Treatment in Neurosyphilis, *J. A. M. A.* **76**:708 (March 12) 1921.

2. Fordyce, J. A.: Results of Treatment in Syphilis of the Nervous System, *Brit. J. Dermat.* **36**:47 (Feb.) 1924.

3. Stokes, J. H., and Shaffer, L. W.: Results Secured by Standard Methods of Treatment in Neurosyphilis, *J. A. M. A.* **83**:1826 (Dec. 6) 1924.

4. Moore, J. E.: The Treatment of Central Nervous System Syphilis, *J. A. M. A.* **89**:588 (Aug. 20) 1927.

5. Hopkins, H. H.: The Incubation Period of Clinical Neurosyphilis, *Arch. Neurol. & Psychiat.* **29**:158 (Jan.) 1933.

6. Head, H., and Fearnside, E. G.: Clinical Aspects of Syphilis of the Nervous System in the Light of the Wassermann Reactions and Treatment with Neosalvarsan, *Brain* **37**:1, 1914.

7. Moore, J. E., and Hopkins, H. H.: The Prognosis of Early and Late Asymptomatic Neurosyphilis, *J. A. M. A.* **95**:1637 (Nov. 29) 1930.

2. Diffuse late neurosyphilis. There is predominant meningeal or vascular involvement, or both, sometimes with and sometimes without parenchymatous changes. This group includes diffuse cerebrospinal syphilis and such widely separated entities as transverse myelitis, syphilitic epilepsy, gumma of the brain, combined system disease and late asymptomatic neurosyphilis.

3. Dementia paralytica and the tabetic form of dementia paralytica.

4. Tabes dorsalis.

5. Optic atrophy.

TABLE 1.—*The Material for This Study*

	Early Syphilis of Central Nervous System	Diffuse Late Syphilis of Central Nervous System	Tabes With Optic Atrophy	Tabes Without Optic Atrophy	Dementia Paralytica and Tabetic Form of Dem. Par.	Optic Atrophy Alone	Vascular Syphilis of Central Nervous System	Total
Died.....	6	54	13	42	71	6	8	200
Observed more than 2 years.....	48	187	23	88	82	35	17	480
Observed less than 2 years.....	65	228	34	65	75	20	32	519
Total.....	119	469	70	195	228	61	57	1,199

TABLE 2.—*Distribution of Cases According to Race and Sex*

	Early Syphilis of Central Nervous System	Diffuse Late Syphilis of Central Nervous System	Tabes With Optic Atrophy	Tabes Without Optic Atrophy	Dementia Paralytica and Tabetic Form of Dem. Par.	Optic Atrophy Alone	Vascular Syphilis of Central Nervous System	Total
Number of patients....	119	469	70	195	228	61	57	1,199
Percentage								
White, male.....	42.9	34.5	55.4	63.8	65.3	32.2	31.6	47.3
White, female.....	11.7	14.4	4.2	16.3	15.1	9.6	3.5	10.6
Black, male.....	30.2	30.8	35.6	12.7	16.0	40.3	49.1	30.8
Black, female.....	15.1	19.6	5.6	7.1	2.6	17.8	15.8	11.9

6. Vascular neurosyphilis. In this group the disease involved only the blood vessels, so far as could be determined.

In analysis of the results, only the 480 patients who were under treatment or observation for two or more years and the 200 who died while under treatment or observation were used. The 480 patients of the former group were 'observed over periods varying from two to twenty years, the average period being approximately ten years.

The distribution according to race and sex is shown in table 2. The predilection of neurosyphilis for the male, especially the white male, is demonstrated again. Of particular interest are the low incidence of parenchymatous neurosyphilis (tabes and dementia paralytica) and the relatively great frequency of vascular neurosyphilis in the Negro race, whereas the distribution of diffuse meningovascular neurosyphilis is approximately equal in the two races.

Table 3 is self-explanatory, confirming the statements concerning the high percentage of asymptomatic infection in patients who develop neurosyphilis.

The much stressed importance of examining the marital partner of the patient suffering from neurosyphilis is reemphasized by the facts presented in table 4. Of 246 partners examined, more than one half were shown to be infected. The relatively greater incidence of conjugal

TABLE 3.—*Percentage of Patients Who Gave a Definite History of Primary or Secondary Syphilis*

	Early Syphilis of Central Nervous System	Diffuse Late Syphilis of Central Nervous System	Tabes With Optic Atrophy	Tabes Without Optic Atrophy	Dementia Paralytica and Tabetic Form of Dem. Par.	Optic Atrophy Alone	Vascular Syphilis of Central Nervous System	Total
Number of patients....	119	469	70	195	228	61	57	1,199
Percentage giving history.....	75.6	48.1	51.4	49.0	46.6	52.4	54.4	54.8

TABLE 4.—*Status of Marital Partner*

	Early Syphilis of Central Nervous System	Diffuse Late Syphilis of Central Nervous System	Tabes With Optic Atrophy	Tabes Without Optic Atrophy	Dementia Paralytica and Tabetic Form of Dem. Par.	Optic Atrophy Alone	Vascular Syphilis of Central Nervous System	Total
Number of patients....	119	469	70	195	228	61	57	1,199
Number of partners examined.....	15	101	10	43	63	8	6	246
Partners with syphilis of central nervous system.....	1	15	0	9	7	2	1	35
Partners with syphilis, not of central nervous system.....	8	23	0	6	4	2	1	44
Partners with syphilis, type questionable....	3	31	1	11	5	3	2	56
Partners syphilitic.....	12	69	1	26	16	7	4	135
Partners nonsyphilitic.	3	32	9	17	47	1	2	111

neurosyphilis in partners of persons with parenchymatous neurosyphilis so often reported could not be confirmed in a study of this type, the data being incomplete.

#### INTERPRETATION OF CHARTS

For simplification and clarity of presentation, the results of treatment have been presented in graphic form. A single chart expresses the results in a single group of cases, favorable results being charted above and unfavorable results below the middle zone, according to the schemes of treatment used. The left vertical half of each chart is



devoted to clinical results, and the right half, to serologic results;<sup>8</sup> at the extreme right may be seen the degree of correlation<sup>9</sup> between the improvement in the physical and that in the serologic status of the patient, under treatment.

The results, favorable and unfavorable, are expressed in percentages, according to six types of treatment as follows:

1. Poor treatment; that is, the patients received less than one year of treatment with the arsphenamines, heavy metals and, in a few cases, tryparsamide.

2. Routine treatment. The patients were given courses of an arsphenamine product, alternating with courses of mercury or bismuth, or both, together with large doses of potassium iodide by mouth given regularly for at least one year. Courses were usually made up of from six to eight weekly injections of the drug. The arsphenamines used were arsphenamine, neoarsphenamine and silver arsphenamine, in decreasing order of frequency.

3. Intensified routine treatment. The group given this treatment received larger doses and longer courses of the arsphenamines, in most cases, old arsphenamine. In some cases the doses were given more frequently than at weekly intervals. Courses consisted of from ten to fifteen injections. As may be seen in chart 1, this type of treatment was used almost solely for patients with early neurosyphilis.

4. Routine treatment to which was added a variable number (from three to fifteen) of intradural treatments by the Swift-Ellis method at intervals of at least two weeks. This was used mostly for the patients with tabes and those with optic atrophy.

5. Routine treatment and tryparsamide. Tryparsamide was used extensively in late neurosyphilis of all types, except in optic atrophy. It was given in doses of from 2 to 3 Gm. at weekly intervals in long courses of from ten to twenty injections. These courses were alternated with courses of bismuth or mercury and also, in some instances, with the arsphenamines.

6. Routine treatment and malaria. Malaria was used largely in the treatment of patients with dementia paralytica, but a few patients with the other types of neurosyphilis were also treated with it. Most of the

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8. Only serologic results relating to the cerebrospinal fluid are considered; no attention is paid to effects of treatment on the Wassermann reaction of the blood.

9. Correlation is expressed as absolute agreement in rate per cent between the clinical and the serologic results of treatment in all the cases in which these results were excellent-excellent, fair-fair, poor-poor, expressed as percentage of the entire group. For example, if of 100 cases excellent-excellent results were obtained in 40, fair-fair in 20 and poor-poor in 20, absolute agreement between clinical and serologic results occurred in 80 per cent.

patients received routine antisyphilitic treatment and many of them tryparsamide either before or after malaria.

The legends on the charts may be defined as follows: Applied to the clinical results, "Excellent" indicates a complete disappearance of symptoms, also of signs not based on permanent degenerative changes such as Argyll Robertson pupils. "Good" means notable improvement in symptoms and signs. "Fair" means slight or no improvement. "Poor" means that the condition became worse. "Dead of Unknown Cause" means that the condition became worse. "Dead of Unknown Cause"

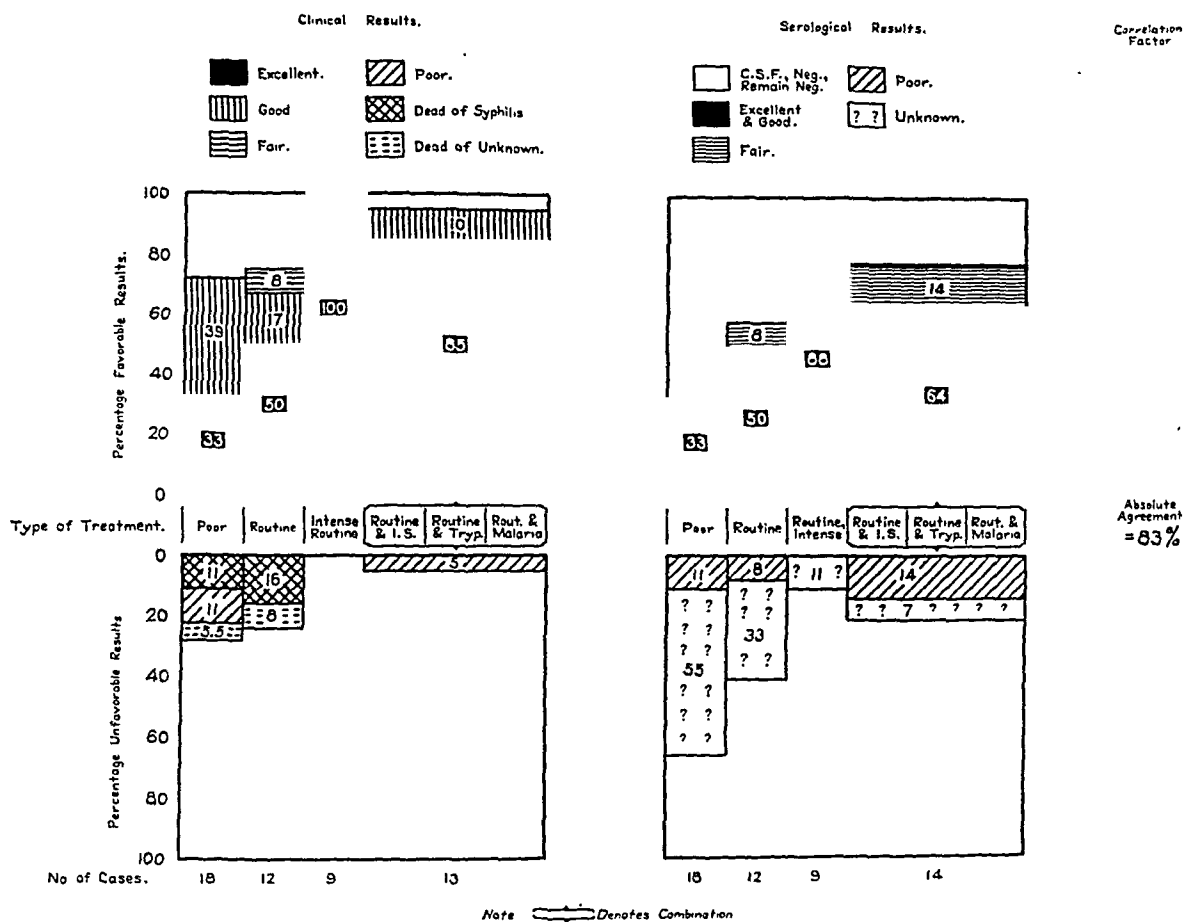


Chart 1.—Serologic and clinical results of six schemes of treatment in early neurosyphilis. The legends are defined in the text.

includes not only all the patients in whom the cause of death was unknown, but also a larger number in whom the cause of death, while known, was unrelated to syphilis. "C. S. F., Neg., Remain Neg." means that on the original examination the cerebrospinal fluid was normal and on subsequent repetition was still normal.

Applied to the serologic results, "Excellent" and "Good" mean that after treatment the spinal fluid became normal or practically so. "Fair" means that after treatment the spinal fluid showed some improvement in its previous abnormalities. "Poor" means that the abnormalities of

the spinal fluid were unaffected by treatment. "Unknown" means that the examination of the spinal fluid was not repeated.

In chart 1, dealing with early neurosyphilis, it will be seen that the best results, both clinical and serologic, were obtained with the intensified form of routine antisymphilitic treatment. The 9 patients so treated showed an excellent clinical response, and in 88 per cent there was an excellent or good serologic outcome. The degree of correlation between the clinical improvement and the serologic improvement in this group of cases was high, absolute agreement being found in 83 per cent. The figures given for the combined group of patients who received intra-

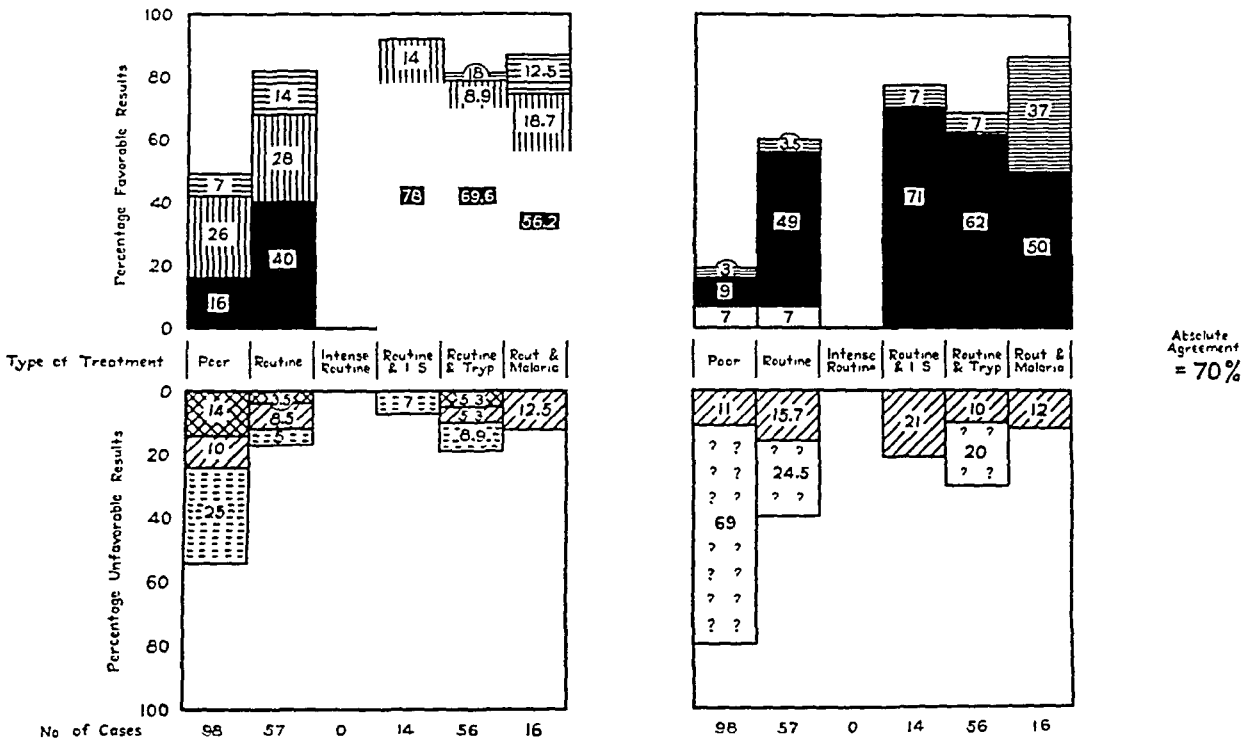


Chart 2.—The results of various types of treatment in diffuse late neurosyphilis.

spinal therapy, tryparsamide or malaria are somewhat misleading, since patients are included in this group who were resistant to previous intensive routine therapy. The fact that many patients with early neurosyphilis need more than routine treatment, however, is well demonstrated.

In chart 2, dealing with diffuse late neurosyphilis, the inadequacy of poor and even of routine treatment is clearly shown. The group who received intraspinal therapy did best (though only a small number of patients are included), and both the group receiving tryparsamide and the one receiving malarial therapy did far better than the patients who received routine treatment. In this group also, a high degree of correlation was noted between clinical and serologic improvement, absolute agreement occurring in 70 per cent.

In chart 3, illustrating the results obtained in dementia paralytica and the tabetic form of dementia paralytica, the superiority of malaria over other forms of treatment in effecting clinical improvement is striking, in spite of the fact that it had less influence on the abnormalities of the cerebrospinal fluid than did intraspinal therapy or tryparsamide.<sup>10</sup> The figures for malarial treatment are even more significant in the light of the fact that a number of the patients in the group treated with malaria had had all other forms of treatment before resort was had to malaria. The low incidence of deaths in the group treated with malaria as compared with that in the other groups is striking. In spite

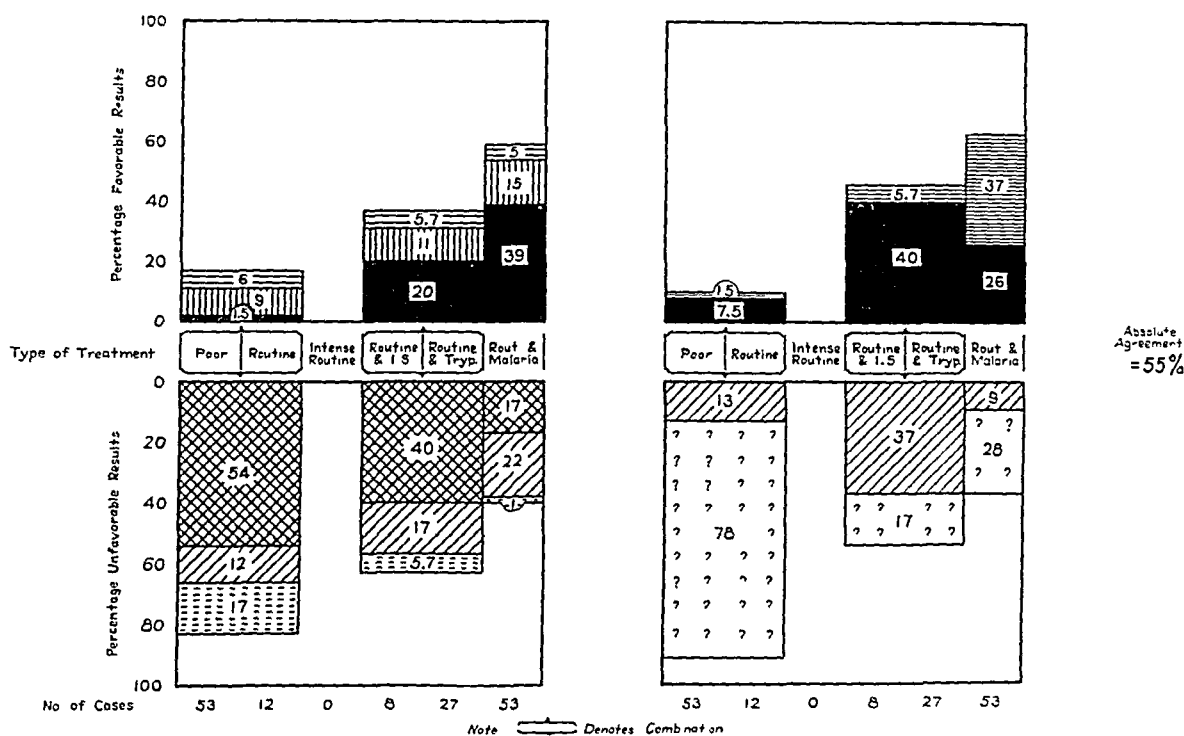
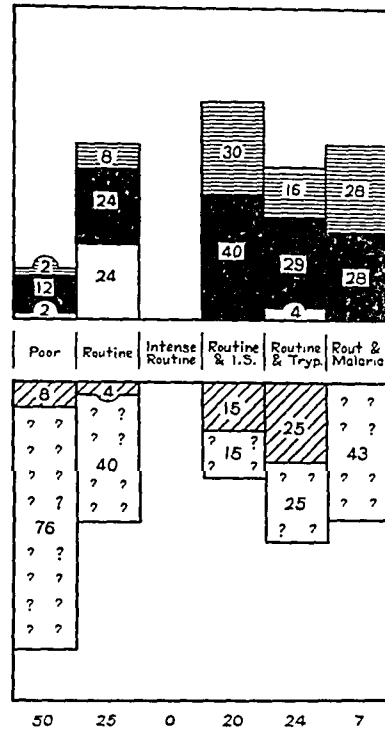
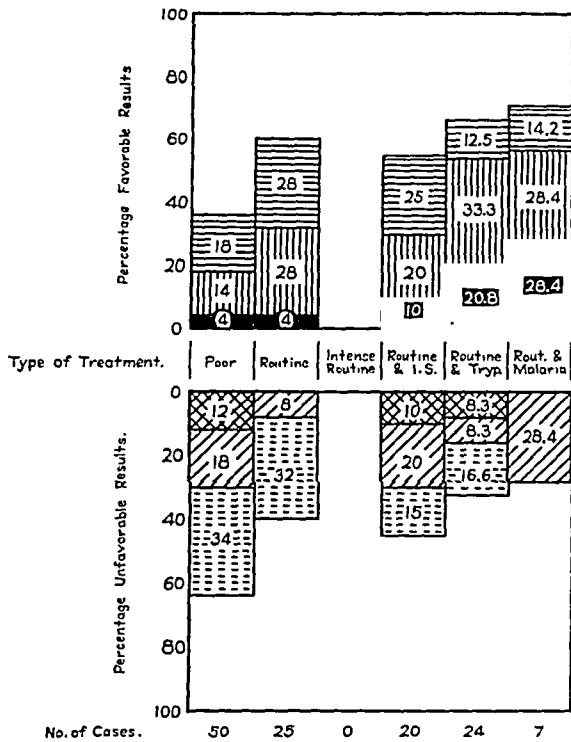


Chart 3.—The results of various types of treatment in dementia paralytica and the tabetic form of dementia paralytica.

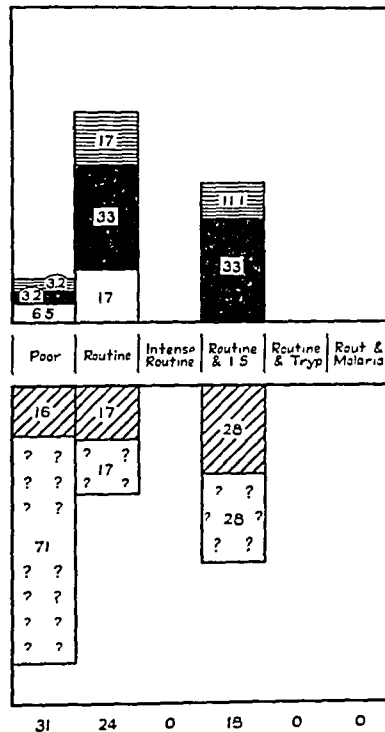
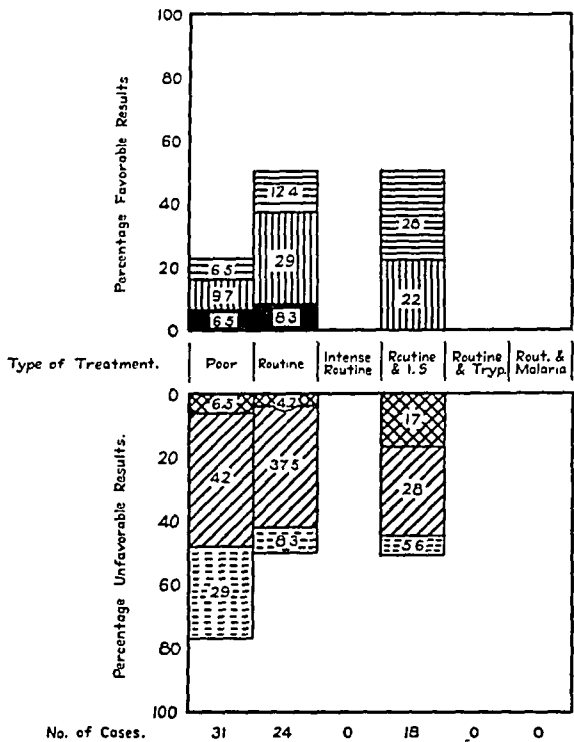
of its preponderantly favorable clinical influence, malaria did not so frequently result in improvement in the condition of the spinal fluid. Absolute agreement was observed in only 55 per cent of the entire group with dementia paralytica. This fact is difficult of interpretation. It suggests that in parenchymatous neurosyphilis the abnormalities of the spinal fluid bear a relation to the associated pathologic changes in the central nervous system different from that in the forms of neurosyphilis which occur earlier in the life history of a person with syphilis; e. g., acute syphilitic meningitis.

10. The results in the groups receiving intraspinal and tryparsamide treatment were combined under one heading because so many of the patients received both forms of treatment. Intraspinal therapy was never given to patients with uncomplicated dementia paralytica, but only to those presenting features of tabes.



Absolute Agreement  
= 40%

Chart 4.—The results of various types of treatment in tabs without optic atrophy.



Absolute Agreement  
= 54%

Chart 5.—The results of various types of treatment in patients with optic atrophy alone and patients with optic atrophy and tabs.

On the whole, the results of the various types of treatment in tabes were similar to those in dementia paralytica. In good clinical results obtained, intradural administration of arsphenaminized serum, treatment with tryparsamide and malarial therapy scaled upward, while in good serologic results, these therapeutic measures scaled downward. Absolute agreement occurred in only 40 per cent. The curious state of affairs observed in parenchymatous neurosyphilis is thus even more striking in tabes than in dementia paralytica. Although the number of tabetic patients treated with malaria was small, the high degree of clinical success obtained with this type of therapy augurs well for its more widespread use.

The results of treatment in the group with optic atrophy are expressed as of optic atrophy alone. Without explanation, the chart gives a false impression of what may be accomplished in this most dreaded complication. The apparent superiority of routine and even of poor treatment shown by the chart is due to the fact that the group treated by the Swift-Ellis method contained those patients in whom optic atrophy progressed in spite of previous antisyphilitic treatment. Thus the 22 per cent good results in the group receiving intraspinal treatment represent slight improvement, and the 28 per cent fair results, arrest in previously progressive atrophy. A detailed analysis of this group of cases appears in a recent paper by Moore.<sup>11</sup>

The number of patients with purely vascular neurosyphilis was so small that no attempt was made to analyze the results in detail. There were only 8 patients who died while under observation and 17 who were observed for periods longer than two years. In general, treatment accomplished comparatively little in the return of function after paralysis had occurred.

#### SUMMARY AND CONCLUSIONS

A study of about 1,200 patients with various forms of neurosyphilis, 200 of whom died while under observation and 480 of whom were observed for more than two years before lapsing, is reported. The percentage of patients who gave a history of early syphilis, the distribution according to race and sex and the status of the marital partners among this group are given. The results of treatment are presented in graphic form according to seven clinical groups of neurosyphilis and six schemes of treatment. The comparative results of treatment under the six plans warrant the following conclusions:

1. In early neurosyphilis the best method of treatment, in our experience, was an intensified form of routine antisyphilitic treatment with arsphenamine.

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11. Moore, J. E.: The Syphilitic Optic Atrophies, *Medicine* **11**:263 (Sept.) 1932.

2. In diffuse late neurosyphilis routine antisyphilitic treatment was much inferior to treatment with arsphenaminized serum subdurally administered, tryparsamide or malaria. The serum gave the best results, but tryparsamide gave almost as good, and owing to the much larger number of patients treated with it, the results probably represent a more nearly exact comparative estimation of its value.

3. In dementia paralytica and the tabetic form of dementia paralytica, malaria was preeminently the treatment of choice.

4. In tabes, the best results were obtained with malaria, although those receiving tryparsamide did almost as well, and both types of therapy were far superior to routine treatment.

5. In optic atrophy, treatment with subdural injections of arsphenaminized serum was successful in arresting the process in numerous cases in which it was advancing in spite of routine methods of treatment.

6. The number of patients with purely vascular neurosyphilis was too small for statistical analysis.

7. In general, the correlation between the clinical and the serologic improvement is roughly proportional to the duration and type of pathologic involvement. In early neurosyphilis, absolute agreement is found in a high percentage, and in parenchymatous neurosyphilis in a correspondingly low percentage, of patients under treatment.

# HYPERINSULINISM

## REPORT OF A CASE OF SPONTANEOUS HYPOGLYCEMIA, WITH STUDIES IN DEXTROSE TOLERANCE

EUGENE ZISKIND, M.D.\*

LOS ANGELES

Spontaneous hypoglycemia is being reported with increasing frequency. The subject was recently reviewed by Gammon and Tenery.<sup>1</sup> The record of a patient who has been under observation for one year follows.

### REPORT OF A CASE

*History.*—A youth, aged 19, a student, was admitted in a state of coma to the Los Angeles County General Hospital on Sept. 8, 1930. For eighteen months prior to admission he had had spells of weakness, headache, trembling and mental confusion occurring at about noon. These the patient attributed to waiting until 1 o'clock for his midday meal. Eating relieved the symptoms. During the eighteen months the patient's weight had increased from 128 to 141 pounds (58 to 64 Kg.). He had not engaged in athletics for one year, because excessive perspiration and a feeling of weakness readily developed on exertion. On September 2, he complained that his mind was a "blank." Three days later he suffered from headache and dizziness. On September 6, he had a series of convulsions involving the right arm and leg, and was semistuporous until 5 p. m. On the next day he had another convulsion, and he remained in coma.

Birth was by forceps delivery. Harelip and cleft palate were repaired at 4 months, and again at 3 years of age. The patient had pneumonia with a convulsion at 2 years; later in childhood he had chickenpox, scarlet fever, measles and influenza with delirium lasting thirty-six hours. There had been many infections of the upper respiratory tract, but none in the last five years. The family history was irrelevant.

*Physical Examination.*—The patient, well developed and well nourished, was in coma. The temperature was 102 F.; the pulse rate, 108, and the respiratory rate, 22. The blood pressure registered 120 systolic and 85 diastolic. Except for the harelip, cleft palate and external hemorrhoids, examination of the head, neck, heart, lungs and abdomen revealed no abnormality. There was right hemiparesis, with hyperactive deep reflexes and a positive Babinski sign on the same side.

*Laboratory Reports.*—No urine was obtained on catheterization, but the blood sugar was 40 mg. per hundred cubic centimeters on two determinations by the

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\* Instructor in neurology, Medical School, University of Southern California.

From the neurologic services of the late Dr. I. L. Meyers and Dr. S. D. Ingham, the Los Angeles County General Hospital.

1. Gammon, G. D., and Tenery, W. C.: Hypoglycemia: Clinical Syndrome, Etiology and Treatment; Report of Case Due to Hyperinsulinism, Arch. Int. Med. 47:829 (June) 1931.



Benedict method.<sup>2</sup> A specimen of urine obtained a few hours later was straw-colored and acid, with a specific gravity of 1.037, and showed albumin, 4 plus; acetone, 2 plus; no sugar, no blood, and many pus cells, with an occasional granular cast. The red blood count was 4,870,000; the white blood count, 11,480, with 67 per cent polymorphonuclear neutrophils, 17 per cent small lymphocytes, 2 per cent large lymphocytes, 7 per cent transitional cells, 3 per cent basophils and 1 per cent eosinophils, and hemoglobin, 97 per cent (Sahli). Examination of the spinal fluid revealed 3 cells per cubic millimeter, a trace of globulin, a normal amount of sugar (rough test) and negative Wassermann, Kahn and colloidal benzoin tests.

No definite diagnosis was made. The day after admission (Sept 9), the patient was transferred to the neurologic service of Dr. I. L. Meyers, still in coma, with a complete right-sided hemiparesis, an inconstant Babinski sign on the left and slight blurring of the nasal margins of both optic disks. The results of the remainder of the neurologic examination were unimportant. The blood sugar was 58 mg. per hundred cubic centimeters; the carbon dioxide combining power, 69 per cent by volume; nonprotein nitrogen, 35 mg., and creatinine, 1.4 mg. Subsequent urinalyses, phenolsulphonphthalein and Mosenthal tests gave negative results. Since the blood sugar was still very low, despite the administration of 150 Gm. of dextrose in the intervening twenty-four hours, I suggested that the coma was probably dependent on the hypoglycemia.

Numerous tests to determine the cause of the hypoglycemia were performed. On the whole, these gave negative results. Spinal puncture (Sept. 16, 1930) gave initial pressure, 160 mm.; no block, 4 cells and no globulin. On Sept. 19, 1930, the findings were the same, except that the pressure was 200 mm. The Wassermann and Kahn tests of both the blood and the spinal fluid were negative. Roentgenograms of the skull on Sept. 11, 1930, and on June 8, 1931, revealed no abnormality. Injections of epinephrine produced a rise in the blood sugar (table 1). The basal metabolic rates were normal:

1931	Basal Metabolic Rate	Blood Sugar
June 11	minus 24	63
June 13	plus 8	56
June 17, 8 a. m.	minus 2	57
June 17, 9 a. m.	plus 8	51
June 17, 10 a. m.	minus 1	53
June 19	minus 4	62

Van den Bergh reactions (direct and indirect), icteric index and determinations of blood calcium (serum and diffusible) were all within normal limits. Blood serum tension, unheated,<sup>3</sup> was 40 dynes per cubic millimeter; heated, 47 dynes per cubic millimeter. Schmidt test meal for external pancreatic function was normal. Roentgenograms of the long bones, chest, gastro-intestinal tract and gallbladder showed that these were normal. A test meal of 70 Gm. protein (cottage cheese and egg white) gave the following blood sugar curve: fasting, 71 mg.; after half an hour, 69 mg.; after one hour and a half, 83 mg.; after two hours and a half,

2. Benedict, Stanley R.: The Estimation of Sugar in Blood and Normal Urine, *J. Biol. Chem.* **68**:759 (June) 1926.

3. Lovell, C.: Surface Tension of Serum in Anxiety Psychoses, *J. Ment. Sc.* **69**:397 (Oct.) 1923. Farran, R. C., and Drury, K. K.: Types of Blood Sugar Curve Found in Different Forms of Insanity, *ibid.* **71**:8 (Jan.) 1925.

83 mg., and after three hours and a half, 64 mg. The blood sugar curve following the oral administration of 100 Gm. of fat (butter and oil emulsion) was: fasting, 56 mg.; after one hour, 58 mg.; after two hours, 53 mg.; after three hours, 52 mg., and after three hours and a half, 122 mg.<sup>3a</sup> A test meal of raw starch (Rosenthal)<sup>4</sup> produced a slight rise in the blood sugar. Attempts to feed a diet low in carbohydrates was unsuccessful because of the frequent hypoglycemic reactions.

The minimal carbohydrate requirement for three days in March, 1931, varied from 474 to 536 Gm., approximately, for each day. This exceeded the amount (360 Gm.) designated by Allan as necessary to compensate for complete loss of function of the liver.<sup>5</sup>

TABLE 1.—*Reactions to Epinephrine*

Date	Amount of Epinephrine 1 to 1,000, Minims	Before Injection		During Injection, Blood Sugar	After Injection	
		Time, Minutes	Blood Sugar		Time, Minutes	Blood Sugar
11/18/30.....	10	20	83	87	10	90
		10	87		20	109
					30	110
1/ 5/31.....	10	10	68	72	10	82
					20	114
					30	104
3/21/31*.....	15	10	66	..	5	66
					20	77
					35	93
					50	90
6/25/31.....	15	5	73	..	60	105

\* Breakfast was eaten at 7:45 a. m. All other tests were taken at least four hours after the last feeding (orange juice).

TABLE 2.—*Metabolic Rates During Dextrose Tolerance Tests*

Date	Test	Fasting	Time After Administration of Dextrose			
			1 Hour	2 Hours	3 Hours	4 Hours
6/13/31	Basal metabolic rate.....	+8	+41	+21	+19	+34
	Blood sugar.....	56	133	164	91	57*
6/17/31	Control, basal metabolic rate...	-2	+8	+1		
	Control, blood sugar.....	57	51	53		
6/18/31	Basal metabolic rate.....	-4	+29	+23	+13	+4
	Blood sugar.....	62	129	128	51	55

\* The patient was very restless.

The effect of dextrose on the metabolic rate is shown in table 2.

None of these tests aided in the elucidation of the etiologic factor for the hypoglycemia.

*Course.*—For the first ten days of hospitalization, the patient was in a coma of fluctuating depth. During this period the variability of the neurologic findings was remarkable. Hemiparesis and some degree of coma were the most constant,

3a. A convulsion occurred after the third hourly specimen.

4. Rosenthal, S. F.: Pancreatic Function and Upper Intestinal Digestion, Arch. Int. Med. 41:867 (June) 1928.

5. Allan, F. N.: Hyperinsulinism: Report of Two Cases, Arch. Int. Med. 44:65 (July) 1929.

and were present at every examination. The Babinski response was present or absent, unilaterally or bilaterally. Rigidity of the neck was inconstant, and the excitability of the tendon reflexes varied. Once there were definite catatonic features. The changing signs were not unlike the picture of cerebral edema so often seen in uremia or eclampsia. In this instance, however, it was probable that the variability of the symptoms was associated with fluctuations in the blood sugar level.

The patient received frequent feedings of dextrose or orange juice by vein and nasal tube. Numerous blood sugar determinations taken just before feedings varied from 50 to 60 mg. On September 19 rigid attempts were first made to keep the blood sugar above hypoglycemic levels at all times during the twenty-four hours. It was calculated that 350 cc. of 10 per cent dextrose administered intravenously at six hour intervals would accomplish this object. Concomitantly, the patient roused to consciousness. It now became apparent that he had aphasia. He was definitely apraxic for a few days. On September 29, there could be demonstrated an anomial aphasia, with some tendency to perseveration. On October 1, the patient was able to cooperate in an examination of the visual fields;

TABLE 3.—*Blood Sugar Readings for Nov. 5, 1930*

Time	Blood Sugar	Comment
8:37 a.m.	76	Headache
9:37	97	Breakfast at 9:30 a. m.
10:37	96	
11:37	105	
12:37 p.m.	77	Headache
1:50	67	Generalized perspiration; tremor of hands; slight weakness of right arm
2:50	65	Restlessness
4:00	61	Pupils dilated; ataxia and tremor more marked, especially on the right; headache intense, greater restlessness
5:00	60	Drowsy; slight headache
6:10	52	Comatose; readily roused

Neurologic examination yielded no findings other than those noted, except the residual visual field defect and the absence of the plantar reflex on the right, which remained unaltered throughout.

he had a right homonymous hemianopia. The diagnosis of a vascular lesion was made; this was probably a thrombosis involving the cortex in the region of the angular gyrus. It was assumed that the lesion was secondary to the hypoglycemia. All the neurologic symptoms showed progressive improvement. The hemiparesis disappeared first, and on October 25, practically all the aphasia was gone. The visual defect cleared slowly; it was eleven months before the fields were again normal.

After the patient regained consciousness, feedings were given by mouth at frequent intervals. His appetite was great. He ate two or three trays of food at each meal and often ate between meals. When the feeding at 2 a. m. was omitted, the patient became mentally disturbed. Once he walked down the fire escape, apparently asleep. At another time, he walked to the center of the ward and urinated on the floor. In the morning, he would deny all knowledge of these episodes.

When recovery from the neurologic symptoms was well advanced, the effect of withholding food was tested. On Nov. 5, 1930, after a light breakfast at 9:30 a. m., the blood sugar level was determined every hour (table 3). When the blood sugar was 52 mg., dextrose was given, since I did not wish to hazard loss of consciousness. Again, on November 22, the patient received no breakfast,

and a blood sugar determination, taken at 10 a. m., was 54 mg. In less than an hour he had a convulsion. It was apparent that the tendency to hypoglycemia still persisted.

The patient was discharged to the outpatient department on Nov. 26, 1930, at which time the only neurologic abnormality was a moderate visual field defect. He was readmitted to the hospital on Nov. 26, 1930, after a convulsion due to the omission of orange juice in the morning.

Since the hypoglycemic tendency was not improving, an abdominal operation was performed by Dr. Walter Bayley on March 26, 1931, in the hope of finding a tumor of the pancreatic islets. At operation, the pancreas was found to be comma-shaped, but normal in appearance and consistency. No tumor mass was seen or felt. The liver was smooth and of normal color and consistency. No tumor was palpated in the region of the suprarenal glands. It had previously been decided to remove about three fourths of the pancreas if no tumor was discovered.<sup>6</sup> Technical difficulty was encountered in that the splenic vein ran through the pancreatic tissue so that very little of the organ could be removed without sacrificing the spleen. Therefore, only 7.2 Gm. of the tail of the pancreas was excised. No abnormalities could be detected in this tissue microscopically. Measurements of the size of the islets were normal. Physiologic assay, which was performed by Dr. D. A. Scott of the University of Toronto, showed that the tissue had "only about one-tenth the amount of insulin present in the pancreas from other sources." The low figure was attributed to deterioration in the acid alcohol. Although fixed in the latter according to instructions previously received from Dr. Scott, the tissue was not sent to Canada until twenty-four days later. Hence this physiologic assay may show far from the actual amount of insulin originally present in the tissue.

As was to be expected, little or no improvement resulted from the operation.

*Thyroid Therapy.*—Since operation failed to effect a cure, it was thought advisable to try the use of certain endocrine products. Because of the apparent antagonism between thyroid secretion and insulin, as shown by the diminished effect of insulin in diabetic patients having hyperthyroidism, thyroid extract was decided on. Janney and Henderson<sup>7</sup> have indicated that hypothyroid conditions are associated with increased tolerance for dextrose, and hyperthyroid states with diminished tolerance. Wagner and Parnas<sup>8</sup> reported that the blood sugar of their patient could be restored to normal by therapy with thyroid.

It should be recalled that my patient presented none of the classic signs of thyroid disease, and the basal metabolic rate was normal. Thyroid, 1 grain (0.06 Gm.) was administered daily by mouth, the dose being increased 1 grain each day. When the patient was taking 34 grains a day (2.2 Gm.), the weight had fallen from 151 to 143 pounds (69 to 65 Kg.), and the metabolic rate had risen to +52. The treatment was discontinued. The blood sugar level was not materially affected by the medication with thyroid. It may be that any tendency of the thyroid to elevate the blood sugar was counterbalanced by the increased utilization of dextrose incident to the rising metabolic rate.

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6. Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of the Pancreas, *Ann. Surg.* **88**:584 (Sept.) 1928. Allan, F. N.; Boeck, W. C., and Judd, E. S.: The Surgical Treatment of Hyperinsulinism, *J. A. M. A.* **94**:1116 (April 12) 1930.

7. Janney, N. W., and Henderson, H. E.: Concerning the Diagnosis and Treatment of Hypothyroidism, *Arch. Int. Med.* **26**:297 (Sept.) 1920.

8. Wagner, R., and Parnas, J. K.: Ueber die Phasen des Kohlehydratumbaues nach Versuchen, die an einem Fall besonderer Kohlehydratstoffwechselstörung angestellt wurden: I, *Ztschr. f. d. ges. exper. Med.* **25**:361, 1921.

Daily injections of an anterior lobe pituitary preparation, 1 cc. daily for a short period, was given because of Wilder's<sup>9</sup> assumption that some instances of spontaneous hypoglycemia are due to deficiency of the anterior pituitary lobe. No improvement was noted, though the drug was not given a long time.

At the end of one year the condition of the patient remained essentially unaltered. There have been ample demonstrations of the hypoglycemic tendency, but control has been easy and reactions occurred chiefly when the frequent feedings were omitted, accidentally or for various tests. The patient was told to eat all he wanted and to have food between meals, and throughout the entire period he was usually awakened for orange juice or egg-nog once or twice during the night. He learned to appreciate signs of oncoming reactions and to ask for orange juice. These attacks were as readily overcome as those of overdosage of insulin. The most frequent premonitory sign was a tingling or numbness of the right hand. In attacks he would present many of the signs noted early after admission, e. g., variations in the Babinski response and tendencies to anomia and perseveration, as well as convulsions and coma. Dilatation of the pupils, excessive perspiration and tremor of the hands were early and almost constant phenomena during attacks. Twice when blood sugar readings were available shortly before and after convulsions, a definite rise in the blood sugar from the hypoglycemic level to normal was noted as a result of the seizure. Only on occasions of hypoglycemia did seizures occur.

Neurologic examinations between attacks gave entirely negative results, except for a persistent defect of the visual field, which was decreasing gradually. When tested on Sept. 16, 1931, the visual fields were normal.

The patient's condition, so far as the hypoglycemic tendency is concerned, is almost the same as it has been for nine months. Since omission of thyroid therapy, his weight has increased to 160 pounds (73 Kg.).

#### COMMENT

The coma, hemiparesis, aphasia and hemianopia, all of which underwent a gradual resolution, indicated a cerebral vascular lesion. The onset of these symptoms during a period of hypoglycemia and their tendency to recur in subsequent hypoglycemic spells suggest that the cerebral lesion was secondary to the lowered blood sugar.

The neurologic symptoms persisted for an unusually long time. Following administration of insulin and in cases of hyperinsulinism, transient nervous phenomena are common. Persisting neurologic manifestation to recur in subsequent hypoglycemic spells suggest that the Ravid<sup>10</sup> reported hemiplegia of three and seven hours' duration after injections of insulin. He also stated that Joslin had seen two patients in whom the paralysis lasted a few days and a few weeks respectively. Hence it is not altogether surprising that in prolonged hypoglycemic states, such as may occur in patients with hyperinsulinism, neurologic

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9. Wilder, J.: Ein neues hypophysares Krankheitsbild: Die hypophysare spontanhypoglykämie, *Deutsche Ztschr. f. Nerven.* **112**:192 (May) 1930.

10. Ravid, J. M.: Transient Insulin Hypoglycemia Hemiplegias, *Am. J. M. Sc.* **175**:756 (June) 1928.

symptoms of long duration may occur. This apparently was the case with my patient.

Of interest are the observations in cases in which a blood sugar determination was secured immediately before and shortly after a convulsion. A postconvulsive rise in the blood sugar to normal or higher levels was demonstrated. This homeostatic significance of hypoglycemic convulsions has been commented on before.

Despite extensive investigations of the endocrine glands, no etiologic factor was found to explain the low blood sugar in this patient. It is, of course, possible that there is an adenoma of the pancreas so situated as to have escaped observation at operation.

#### STUDIES IN TOLERANCE OF DEXTROSE

Diabetes mellitus and hyperinsulinism presumably represent opposite secretory states of the pancreatic islets: the former, hypo-activity, and the latter, hyperactivity. In diabetes, hypo-insulinism, there is a decreased tolerance for carbohydrates. In hyperinsulinism one would therefore expect an increased tolerance.<sup>11</sup> However, in most of the cases of lesions in the pancreas or liver the dextrose tolerance curves were similar to those seen in diabetes (table 4). The explanation of this striking fact attracted my attention. Very little discussion on this subject is to be found in the literature. The attitude usually expressed is that a perverted pancreatic secretion, dysinsulinism, is present. Wilder and others<sup>12</sup> found at necropsy an excessive amount of glycogen in the liver of their patient. Hence they interpreted the curves showing a prolonged high blood sugar as being due to inability of the liver to store more sugar, since its glycogen capacity was saturated. Wagner and Parnas<sup>8</sup> assumed that there existed a disturbance of the normal storing capacity of the liver for dextrose. They thought, however, that it was the glycogen-storing function of the liver that was primarily impaired, so that the amount of glycogen in the liver was less than normal.

In view of the conformity of the rest of the clinical picture to that which might be expected in true hyperinsulinism, the value of the dextrose test by mouth as an index of tolerance was questioned. Variations in the rate and degree of absorption of dextrose from the intestinal tract might influence the test<sup>13</sup> and thus introduce an error in the

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11. Harris, Seale: Hyperinsulinism and Dysinsulinism, *J. A. M. A.* **83**:739 (Sept. 6) 1924.

12. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, E. A.: Carcinoma of the Islands of Pancreas; Hyperinsulinism and Hypoglycemia, *J. A. M. A.* **89**:348 (July 30) 1927.

13. Beeler, C.; Bryan, A. W.; Cathart, E. P., and Fitz, R.: An Improved Alimentary Glucose Tolerance Test, *J. M. Research* **1**:549, 1922.

interpretation of dextrose tolerance. This has been vigorously denied.<sup>14</sup> It was nevertheless decided to rule out this possibility by an intravenous test.

Following the technic used by Lennox and Bellinger<sup>15</sup> (0.3 Gm. of dextrose per kilogram of body weight in a 20 per cent solution

TABLE 4.—*Dextrose Tolerance Curves in Cases of Hyperinsulinism*

Author	Fasting	Time After Administration of Dextrose				
		½ Hour	1 Hour	2 Hours	3 Hours	4 Hours
Carr et al.: J. A. M. A. (February 7)	81	134	132	135	102	
96:1363 (Apr. 25) 1931 (March 18)	81	161	172	119	101	62
Finney and Finney <sup>c</sup> .....	79	232	196	192		
	52	192	...	135*	111†	
Howland et al.: Carcinoma of Pan- creas, J. A. M. A. 93:674 (Aug. 31) 1929 .....	80	160	230	260	240	
Nadler and Wolfer: Carcinoma of Liver, Arch. Int. Med. 44:700 (Nov.) 1929 .....	45	...	209	206	158	
Wilder et al.: Carcinoma of Pan- creas <sup>12</sup> .....	68	242	283	223	70	
Womack et al.: J. A. M. A. 97:631 (Sept. 19) 1931.....	100	175	210	170	165†	
Ziskind .....	9/11/30	51.9	109	166	222	
	11/12/30	77	144	144	157	
	11/20/30	65	114	116	122	56
	1/ 8/31	58	133	120	142	93
	4/ 3/31	75	183	232	141	94
	6/13/31	56	...	133	164	91
	6/19/31	62	...	129	128	51
						43

\* 1½ hours.

† 2½ hours.

TABLE 5.—*Intravenous Dextrose Tolerance Tests*

Author	Date	Fasting	Time After					
			4 Min.	15 Min.	30 Min.	45 Min.	60 Min.	2 Hr.
Ziskind.....	3/16/31	51	303	146	99	78	66	
	3/24/31	65	222	194	160	65	60	65
	4/11/31	70	202	133	...	87	70	54
Lennox (average normal)...	.....	100	222	150	120	90	95	
Control.....	4/11/31	142	185	191	157	131	112	76

administered over a period of four minutes), a number of intravenous tests were made on the patient. The results (table 5) did not show a

14. Joslin, E. P.: The Treatment of Diabetes, Philadelphia, Lea & Febiger, 1928, p. 200.

15. Lennox, W. G., and Bellinger, M.: Comparison of Blood Sugar Curves Following Ingestion and Intravenous Injection of Glucose, Arch. Int. Med. 40:182 (Aug.) 1927.

definitely decreased tolerance as compared with the intravenous curves of Rigler<sup>16</sup> in diabetes; neither did they suggest increased tolerance.

The continuous intravenous method of Woodyatt<sup>17</sup> for determining tolerance for dextrose was employed next. This I believe to be the most accurate known means of measuring the tolerance for dextrose. Woodyatt states that tolerance for dextrose depends on the rate at which the tissues are able to abstract a known amount of dextrose from the blood by their combined powers to burn it, to reduce it into fat or to polymerize it into glycogen, and should be expressed as a velocity in grams of dextrose abstracted from the circulation for each kilogram of body weight for a unit of time. Woodyatt found the normal tolerance to be 0.8 Gm. of dextrose per kilogram of body weight during an hour. When dextrose was administered continuously by vein by means of the Woodyatt pump, the figures obtained for the patient whose case has been reported were approximately 1.3 Gm. per kilogram of body

TABLE 6.—*Results with Woodyatt Dextrose Pump*

Time	Amount 20 per Cent Dextrose per Hour, Cc.	Dextrose per Kg. of Body Weight per Hour, Gm.	Blood Sugar	Urinary Sugar, per Cent
Fasting.....	...	...	57	
7:00 to 7:30 a.m.....	200	0.7	119	0
7:30 to 8:00.....	240	0.8	158	0
8:00 to 8:30.....	312	1.0	186	0
8:30 to 9:00.....	400	1.3	256	0.5

weight an hour (table 6). This represented an increased tolerance of 63 per cent and is more consistent with the type of tolerance to be expected in hyperinsulinism. If similar results are obtained in other cases, the dextrose test by mouth should be discarded as a true index of tolerance, and the presence of an increased tolerance in hyperinsulinism should be accepted as a fact.

The explanation for the different curves obtained by the intravenous and oral methods, though possibly bound up with the question of intestinal absorption, is not clear. Beeler and others<sup>18</sup> showed that when the dextrose was administered orally, from 22 to 68 per cent could be aspirated from the stomach at the end of the first hour. In the case reported in this article aspiration of the stomach contents

16. Rigler, L. G., and Ulrich, H. L.: Blood Sugar Reaction Following Intravenous Injection of Glucose, *Arch. Int. Med.* **32**:343 (Sept.) 1923.

17. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, *J. A. M. A.* **65**:2067 (Dec. 11) 1915; The Method of Timed Intravenous Injections, *J. Biol. Chem.* **25**:355 (March) 1917.



one hour after the dextrose was given resulted in a marked fall in the blood sugar, but this also happened subsequently in controls (without aspiration). In control tests hyperglycemia did not follow the ingestion of sugar; this can possibly be explained on the basis of overstimulation of the insulin-secreting mechanism by repeated dextrose tests.<sup>18</sup>

#### SUMMARY

1. A case of spontaneous hypoglycemia is presented, with observations over a period of one year. This case is unique in that a cerebral vascular lesion presumably due to the hypoglycemia was present and persisted for a long time.

2. No abnormality in the pancreas was noted at operation. Clinical investigation of the endocrine glands did not reveal a causative agent for the hypoglycemia.

3. No improvement resulted from therapy with thyroid.

4. An increased tolerance for carbohydrate was revealed by the intravenous dextrose test of Woodyatt, whereas the oral dextrose test indicated a decreased tolerance. In view of the greater validity of the Woodyatt test, the increased tolerance shown by this test may represent the true state of carbohydrate tolerance in these cases.

In the study of this case, the author has availed himself freely of all the facilities for consultation and of the cooperation of the various specialty departments at the Los Angeles County General Hospital. Dr. Newton Evans, pathologist at the hospital, secured for me the cooperation of the laboratory. Mrs. R. Bolton made assiduous efforts in securing basal metabolic rates on a patient with harelip. Dr. A. Chaney, hospital chemist, and Miss L. Giebelstein, dietitian, assisted in the management of this case.

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18. Lennox, W. F.: Stimulation of the Sugar-Regulating Mechanism as Shown by Duplicate Blood Sugar Curves, *J. Biol. Chem.* **73**:237, 1927.

# BLOOD CHOLESTEROL IN THYROID DISEASE

## II. EFFECT OF TREATMENT

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In part I of this study, the blood cholesterol values found in different types of thyroid disease were presented. This report deals with the effect of preoperative and operative treatment. The cases dealt with herein comprise those in which postoperative myxedema did not occur. Cases in which myxedema did occur will be dealt with in part III of this study. On the other hand, cases with postoperative low metabolic rates but without clinical evidences of low thyroid function are included.

### EFFECT OF PREOPERATIVE AND OPERATIVE TREATMENT

*Effect of Preoperative Treatment in Exophthalmic Goiter.*—It was shown in part I that patients who had received iodine before coming under observation had a higher average value for cholesterol and a lower average basal metabolic rate than those who had not. Preoperative preparation, which consisted mainly of the administration of 30 minims (1.9 cc.) of compound solution of iodine daily, an adequate amount of fluid and a high caloric diet, was carried on from six to fourteen days. As a rule, a second basal metabolic rate was taken on the sixth day, at which time the blood was taken for cholesterol analysis. In table 1 are shown the results in sixty-eight cases of exophthalmic goiter, in which one-half of the patients had received iodine before admission to the hospital and one-half had not. The effect of preoperative treatment was, on the whole, greater in the latter group, as shown by the lowering of the basal metabolic rate and the elevation of the blood cholesterol.

That patients improve more rapidly when they have not received iodine before preoperative iodination has been noted by many on clinical observation and on study of the basal metabolic rate. Confirmation of this by cholesterol studies is of interest.

*Effect of Preoperative Regimen of Iodine on Toxic Adenomatous Goiter.*—The effect of compound solution of iodine was noted in eight cases; the average values are shown in table 2. There was an increase in cholesterol in every case but two, in both of which compound solution

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of iodine had been given for only a few days and in one of which the condition was complicated by diabetes mellitus.

*Immediate Effect of Hemithyroidectomy or Subtotal Thyroidectomy.*—The data illustrating the effect of operation are given in detail in tables 3 and 4. The averages are shown in charts 1 and 2. It will be

TABLE 1.—*Effect of Preoperative Treatment on Level of Blood Cholesterol in Exophthalmic Goiter*

	Before Treatment				After Treatment			
	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
A. Patients with history of iodine administration before admission to hospital; average in 34 cases .....	45.3	104.0	124.9	127.0	33.4	96.6	125.8	141.8
B. Patients without history of iodine administration before admission to hospital; average in 34 cases.....	55.0	105.0	122.2	123.5	32.0	93.2	124.4	144.0

TABLE 2.—*Toxic Adenomatous Goiter: Results of Preoperative Treatment (Iodine) in Eight Cases*

		Before Treatment				After Treatment			
Days of Treatment	Number	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
10	1	40	104	122	122	21	84	122	207
4	2	87	152	134	132	63	128	135	165
5	3	17	72	115	156	5	66	118	172
5	4	50	104	108	121	36	104	104	148
5	5	30	118	155	125	27	112	150	149
4	6	80	144	112	158	62	136	110	148
5	7	26	98	113	152	28	80	114	150
10	8	Too sick to take B.M.R.			88	27	86	113	143
Total.....		330	792	859	1,054	269	796	966	1,282
Average.....		47	113	123	132	34	99	121	160

noted that six days after operation there is an average rise of the cholesterol content over that before operation. There are exceptions; because of postoperative thyroid and febrile reactions, some patients may show a marked drop in the cholesterol content of the blood. At this point of observation there is less correlation between the cholesterol value and the basal metabolic rate than at any other time. Infection tends to lower the cholesterol value, as will be shown later.

*Values at Intervals of from Three to Twelve Months After Operation.*—In tables 3 and 4 are shown values obtained at various intervals

TABLE 3.—Cholesterol Content of the Blood

Date	Sex	Age	Duration, Months	Weight Loss in Pounds	On Admission to Hospital				Before Operation				Six Days After Operation				
					Iodine Before Admission	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.
1/15/31	F	18	..	5	+	25	126	113.5	93	19	120	117.0	123	14	94	113.5	99
1/12/31	F	33	12	15	+	50	118	143.7	94	38	86	144.5	117	24	80	141.0	148
1/27/31	F	39	12	18	+	31	96	112.0	101	34	102	112.7	136	21	88	109.0	129
1/19/31	M	50	24	27	0	48	90	134.7	102	10	89	134.5	124	6	76	133.0	119
1/16/31	F	43	12	10	0	37	98	100.2	156	21	92	104.0	105	16	104	102.0	165
1/18/31	F	24	2	15	0	62	110	109.0	132	2	86	111.5	182	3	70	108.0	174
1/24/31	M	36	3	3	+	13	76	155.0	104	2	76	158.0	177	13	79	153.0	144
1/14/31	F	21	?	3	+	47	100	106.7	110	19	84	107.2	129	4	80	106.0	150
1/2/31	M	24	?	6	+	45	108	122.0	138	47	88	123.7	119	11	100	123.0	119
1/24/31	M	29	24	40	..	30	76	155.0	119	11	98	162.0	175	0	72	159.0	164
1/4/31	F	46	6	10	+	44	118	116.0	102	24	110	111.7	120	6	76	125.0	151
1/1/31	F	19	12	6	0	49	100	111.5	117	53	116	112.0	159	2	80	113.0	189
1/29/31	F	20	12	4	0	41	99	108.7	149	28	92	111.0	143	7	78	108.5	159
1/19/31	F	37	8	10	+	29	86	120.5	133	37	94	124.0	114	13	88	116.0	110
1/13/31	F	42	3	31	+	34	108	101.0	176	38	112	102.0	168	16	90	100.5	227
1/28/31	F	45	?	0	+	34	110	128.7	98	31	112	130.0	122	27	122	125.0	161
1/26/31	F	30	..	12	0	67	96	126.0	121	34	94	129.5	182	21	88	125.0	147
1/9/31	M	38	12	36	0	38	94	133.0	134	8	84	138.7	152	10	94	137.0	128
1/26/31	F	49	4	34	0	44	94	95.5	105	33	80	93.7	154	10	86	94.5	200
2/19/31	F	21	..	6	0	35	114	124.5	150	48	86	122.5	159	9	110	120.0	149
2/6/31	F	20	3	5	+	27	98	110.0	149	24	96	113.7	142	29	80	110.0	191
2/17/31	F	43	3	10	+	51	112	117.0	121	22	96	119.5	187	..	...	.....	...
1/9/31	F	33	..	7	+	31	90	103.0	174	25	120	103.0	212	9	96	104.0	181
3/2/31	M	34	..	..	+	65	108	150.0	99	45	94	157.0	114	..	...	.....	...
4/1/31	F	37	9	23	+	37	100	136.0	111	..	...	.....	...	8	92	125.0	151
al.....		831	159	336		1,014	2,525	3,033.2	3,088	653	2,307	2,943.4	3,520	267	2,023	2,751.0	3,555
average.....		33.2	9.3	14		40.5	101	121.3	123.5	27.2	96.1	122.6	146.6	11.6	87.9	119.6	154.5

TABLE 4.—Effect of Two-Stage Operation

Date	Sex	Age	Duration, Months	Weight Loss in Pounds	Iodine Before Admission	On Admission				Before First Operation				After First Operation				Before Second Operation			
						Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.
1/23/31	F	50	14	50	+	69	92	117.0	199	41	92	118.5	179	..	..	.....	...	37	96	128.7	154
1/14/31	M	46	12	47	0	38	118	155.0	129	5	80	157.0	186	14	84	153.0	151	6	80	168.5	128
1/11/31	F	62	?	15	?	34	110	96.5	128	41	104	95.5	145	..	..	.....	...	21	98	106.0	186
1/2/31	F	63	2	35	0	49	94	130.0	161	..	..	.....	...	..	..	.....	...	38	92	138.0	169
1/9/31	M	49	8	25	+	39	90	152.0	...	30	96	152.0	169	..	..	.....	...	14	90	157.7	162
1/14/31	M	44	2	30	+	65	100	138.0	128	57	114	140.0	132	..	..	.....	...	19	98	151.0	115
1/7/31	F	32	6	15	0	43	116	122.7	133	17	104	122.5	168	+2	80	120.0	158	5	82	128.0	145
1/13/31	F	51	168	..	+	61	103	115.5	166	18	94	117.0	181	42	120	116.5	174	31	112	123.7	167
1/19/31	F	31	6	14	0	62	112	78.0	122	57	90	78.0	203	23	106	77.0	213	39	100	87.0	145
1/24/31	F	31	2	35	0	74	118	150.5	85	60	94	150.2	117	41	92	147.0	142	60	124	146.0	63
1/7/31	F	36	..	0	?	67	120	141.0	99	39	98	142.5	112	35	98	140.0	136	8	92	146.0	133
1/20/31	F	28	6	9	0	83	132	102.0	95	55	128	102.5	126	..	..	.....	...	58	130	115.0	91
1/4/31	F	65	6	40	?	63	106	144.0	...	42	104	144.5	135	35	108	142.0	144	47	118	150.0	134
1/24/31	F	19	6	?	?	74	142	168.0	71	..	...	.....	...	..	...	.....	...	29	110	168.0	105
1/24/31	F	40	6	15	0	56	100	109.7	125	..	...	.....	...	..	...	.....	...	29	79	113.7	162
1/29/31	F	17	6	30	+	61	132	146.0	120	..	...	.....	...	39	118	136.7	115	31	128	154.0	151
1/21/31	F	49	3	20	+	67	100	129.0	96	34	90	129.0	103	25	84	122.5	128	55	96	129.5	155
1/12/31	F	34	14	19	+	104	124	115.7	85	..	...	.....	...	46	76	111.5	96	38	76	124.0	156
4/10/31	M	49	60	15	+	34	98	125.0	162	45	98	127.5	152	..	...	.....	...	4	76	140.0	150
total.....		796	325	414		1,143	2,112	2,435.6	2,104	531	1,386	1,176.7	1,952	274	966	1,266.2	1,457	559	1,877	2,574.8	2,671
average.....		42	19	26		60	111	128.2	124	31	99	126.9	151	27	96	126.6	145	29	99	135.5	141

Before and at Varying Periods After Operation

Three Months After Operation				Six Months After Operation				Nine Months After Operation				One Year After Op		
Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds
-8	80	114.0	140	-6	76	114.7	132							
-9	56	160.0	140											
+3	66	122.0	157	+5	72	125.7	177							
-2	65	151.0	126	-5	62	112.0	148	-8	72	110.0	159	+2	68	112.0
-11	58	110.5	250											
+3	68	121.0	208	+5	72	125.0	177							
-11	79	177.0	179	-2	62	173.7	159	...	..	.....	...	+5	66	176.0
-8	60	117.5	186											
+20	68	157.0	111											
+3	69	172.0	131											
+7	80	134.0	144											
-7	68	119.0	227											
-4	80	129.0	158	....	..	.....	...	-11	66	132.0	143			
+4	80	114.0	207	+7	72	117.5	234	-9	72	116.0	228	+9	72	115.0
-10	70	129.0	182											
0	80	140.0	195											
-17	68	155.7	147	-6	75	165.0	182	+3	77	168.0	162	+3	72	168.0
								-1	78	124.0	186			
+10	70	129.0	156	+18	70	128.0	150	-3	70	128.0	174			
-5	88	117.0	147*	-11	86	113.7	160							
-10	72	128.0	152	-16	68	127.0	120	-4	80	133.0	149	+4	72	131.0
+6	106	117.0	216	+5	80	115.0	196							
-5	72	188.0	144	-7	64	192.0	140							
-15	76	147.0	182	-17	68	158.0	173	-4	80	151.0	169	-11	68	157.0
-66	1,679	3,148.7	3,885	-30	927	1,767.3	2,148	-37	595	1,062.0	1,370	+12	418	859.0
-2.9	73	136.9	169	-2.3	71.3	135.9	165.2	-4	66	118.0	171	+2	69	143.1

on Cholesterol Content of the Blood

After Second Operaiton				Three Months				Six Months				Nine Months				One Year		
Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds
19	84	124.0	148	-10	80	127.7	195	-11	74	127.0	156							
0	88	168.0	151	-33	66	180.0	158	14	58	189.0	180							
8	104	104.0	179	-4	88	116.7	250	..	..	.....	...	....	..	...	...	+20	74	112
..	...	.....	...	4	62	150.0	208	0	78	168.0	195	....	..	...	...	-4	68	173
..	...	.....	...	2	90	157.0	143	2	70	175.0	247							
..	...	.....	...	-14	60	172.0	169	-9	66	176.0	179							
15	92	116.5	156	-5	68	131.5	152	8	88	132.0	139	+8	88	132	139			
22	120	118.7	174	13	84	132.0	179											
4	94	86.5	161	-10	72	96.0	248											
32	90	141.0	110	11	76	164.0	142	..	..	.....	...	+17	92	179	123			
6	80	143.7	123	-16	62	152.0	171	-14	62	150.0	153							
9	80	111.7	120	21	80	123.0	136	-1	90	124.0	145	....	..	...	...	-14	76	125
16	104	147.0	142	9	96	167.0	157											
15	94	162.0	137	-7	86	172.0	181	-10	76	155.0								
10	80	111.0	171	-7	76	121.0	96	-12	76	125.7	134	-12	70	123	118			
..	...	.....	...	-9	80	181.0	174	-6	88	187.0	152							
..	...	.....	...	2	64	145.0	160											
..	...	.....	...	2	68	128.0	134	8	68	124.0	154	....	..	...	...	-7	64	151
..	...	.....	...	-23	78	151.0	161	-9	70	157.0	157	....	..	...	...	-3	66	148
156	1,110	1,534.1	1,772	-74	1,436	2,766.9	3,214	-16	902	1,989.7	1,991	+13	250	434	350	-8	348	703
13	93	127.8	148	-4	76	145.6	169	-1	74	153.1	165	+4	83	144	126	-2	69	141

following subtotal thyroidectomy performed by one-stage and two-stage operations. The effect on blood cholesterol and that on basal metabolic rate six weeks after hemithyroidectomy are comparable; the percent-

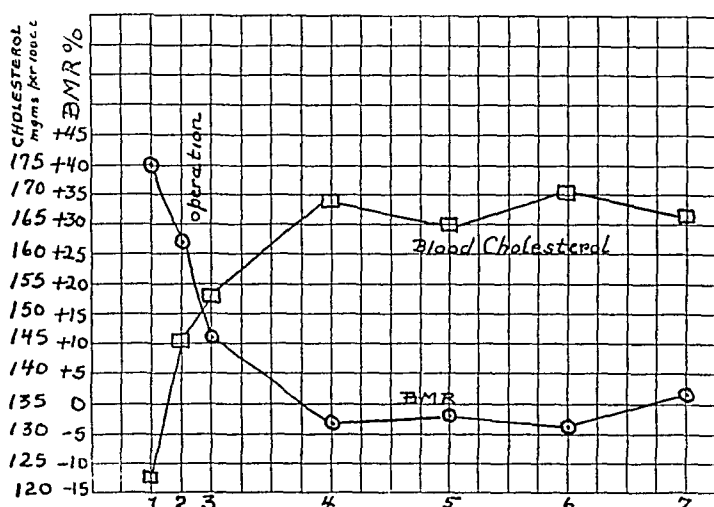


Chart 1.—Effect of preoperative treatment and subtotal thyroidectomy on the basal metabolic rate and blood cholesterol (averages of values found in cases listed in table 1); 1, on admission to the hospital; 2, after preoperative treatment; 3, six days after operation, and 4, 5, 6 and 7, three, six, nine and twelve months, respectively, after operation.

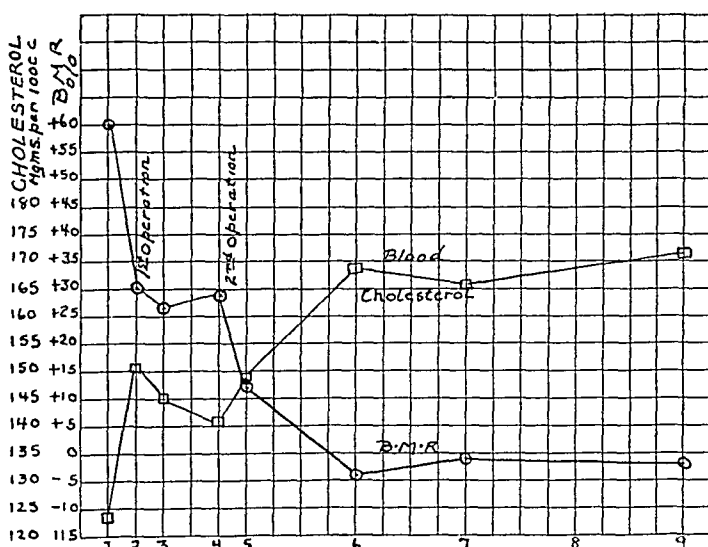


Chart 2.—Effect of subtotal thyroidectomy done in two stages on the basal metabolic rate and blood cholesterol (average values from table 2); 1, on admission to the hospital; 2, after preoperative treatment; 3, six days after hemithyroidectomy; 4, six weeks later, before second stage operation; 5, six days after second stage operation, and 6, 7, 8 and 9, three, six, nine and twelve months later, respectively.

age of drop in the basal metabolic rate and the percentage of elevation in cholesterol are approximately half the change in basal metabolic rate

and cholesterol three months following subtotal thyroidectomy done in one stage. This steplike result shows conclusively that more than a hemithyroidectomy is necessary to end hyperthyroidism.

In table 5, the average values for patients followed for three, six and twelve months are given. It was not felt necessary to present the complete data in these cases, as they added nothing to the data in tables 3 and 4. The obtaining of cholesterol values was not complete in these cases following preoperative treatment or immediately after operation, and they were therefore not included in tables 3 and 4.

TABLE 5.—*Exophthalmic Goiter*

A. One-Stage Operation: Results at Three and Six Months																
Number of Cases	Before Operation				Three Months After Operation				Six Months After Operation							
	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
68	42	110	120	126	—4	74	135	162								
21	39	103	123	141	—2	76	137	161	—1	77	133	164				

B. Two-Stage Operation: Results Before First and Second Operation and at Three and Six Months																
	Before First Operation				Before Second Operation				Three Months After Second Operation				Six Months After Second Operation			
	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
18	53	107	128	116	29	93	131	149	—2	74	140	177				
13	64	113	128	131	26	94	137	139	—8	72	147	158	—3	76	145	159

C. Results Before Operation and at End of Twelve Months																
	Before Operation				At End of Twelve Months											
	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
16	48	104	127	127					+1	70	147	171				

Of the cases observed at the end of three months, eight of sixty-eight (not included in tables 3 and 4) showed a lower cholesterol value after operation than before. The greatest drop was from 126 to 53 mg., the drop in the remainder averaging 17 mg. No explanation could be found for these variations. In the group followed for six months, six of the twenty-one showed a lower value three months after operation, while at six months three of these showed values above those noted before operation. At six months nine cases showed lower values than at three months, although they were well above those found before operation. At twelve months, only one patient showed a lower value than that noted before operation.

In chart 3 is shown the smoothed frequency curve in eighty-nine cases before, and three months after, operation. The shift to the right

is obvious, and the "scatter" appears to be greater. This is due chiefly to the fact that higher cholesterol values are found after operation than can rightly be considered normal. A discussion of these higher values will be taken up in the last paper of this study.

In cases in which operation was not followed by persistent hyperthyroidism or myxedema, there appears to be two types of change in the cholesterol values. 1. There is an abrupt rise at the end of three months, occasionally above normal limits, which tends to drop on subsequent observations. In these cases, no evidence of thyroid deficiency appears, as the patient has no complaints. 2. The second type of change is that characterized by a less abrupt increase, followed by increasing values as time goes on and occasionally followed by myx-

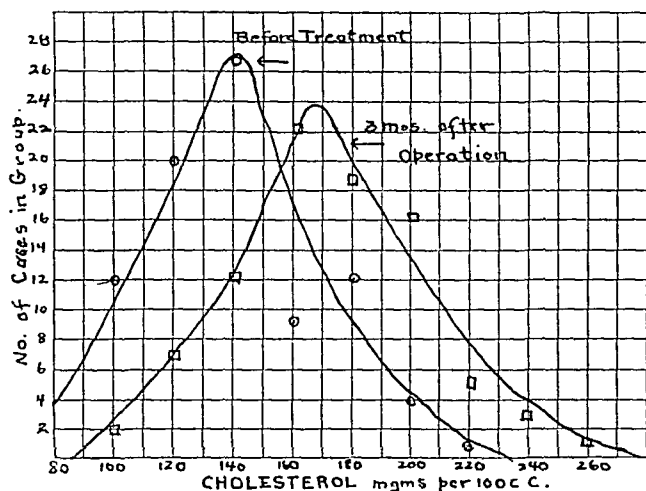


Chart 3.—Smoothed frequency curve of cholesterol value in eighty-nine cases of exophthalmic goiter before treatment and three months after subtotal thyroidectomy. It is to be noted that the "scatter" is greater following operation, and that the peak of the curve has shifted to the right.

edema. Clinical observation reveals that most cases of postoperative myxedema are well established at the end of three months.

*Results in Toxic Adenomatous Goiter After Operation.*—Thirty-three cases of toxic adenomatous goiter were observed three months after operation. The complete data are included in table 6. Four other cases were checked up twelve months after operation, and the values were all under 200 mg. per hundred cubic centimeters. In only one case of toxic adenomatous goiter seen after operation did hypothyroidism develop. Several cases with rather severe diabetes were encountered. Low cholesterol values were the rule before operation in these cases just as in those without diabetes.

*Results in Nontoxic Goiter After Operations.*—As a check on the values found in hyperthyroidism, seventeen patients who had had



adenomas or adenomatous goiter were examined from three to twelve months after operation. In these seventeen cases, before operation the average cholesterol value was 198 mg. per hundred cubic centimeters of blood, while after operation the average value was 202 mg. Although a comparison between the values found in persons with toxic

TABLE 6.—*Toxic Adenomatous Goiter: Results in Thirty-Three Cases Before and Three Months After Operation*

No.	Sex	Age	Before Treatment			After Treatment			Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
			Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds			
1	F	58	40	104	122	-15	56	140		172	
2	F	53	45	96	154	-13	66	164		236	
3	M	45	44	96	151	+6	60	170		139	
4	F	59	48	104	91	+2	88	127		186	
5	F	49	25	86	113	+1	64	119		194	
6	F	64	50	104	108	-7	72	141		184	
7	F	58	14	90	76	-5	70	88		180	
8	F	50	44	88	138	-13	68	156		122	
9	F	34	37	150	107	-6	68	120		121	
10	F	34	41	92	119	+18	84	125		146	
11	F	58	30	118	155	+15	76	151		186	
12	F	58	58	96	122	-9	68	146		181	
13	F	44	40	108	118	-5	88	138		214	
14	F	58	35	120	119	+6	66	135		147	
15	F	49	33	88	170	+8	84	182		165	
16	F	39	35	96	176	-6	82	186		187	
17	F	44	25	118	118	-6	84	132		156	
18	F	55	39	98	132	0	76	144		233	
19	F	48	50	116	147	-5	80	165		192	
20	M	59	25	80	138	-10	59	151		195	
21	F	65	33	80	108	-12	58	116		162	
22	F	56	36	114	143	+2	78	130		140	
23	F	60	50	98	80	-23	80	92		245	
24	F	28	40	98	119	-5	90	143		167	
25	F	64	27	90	110	-6	62	108		196	
26	F	58	54	112	100	+18	84	118		186	
27	F	33	30	98	109	+2	80	122		180	
28	F	35	31	126	124	-15	60	129		192	
29	F	19	15	104	102	-13	90	104		135	
30	M	40	24	98	145	+17	74	155		213	
31	F	65	28	98	112	0	62	121		208	
32	F	34	19	90	202	+7	88	209		212	
33	F	56	16	94	92	+5	76	100		227	
Total.....		1,629	1,161	3,348	4,120	-67	2,441	4,527		6,002	
Average....		49	35	102	122	-2	74	137		182	

goiter and those found in persons with nontoxic goiter showed an average difference of from 40 to 50 mg., the preceding figures help to confirm the impression that the amount of thyroid secretion is the main factor influencing the level of the cholesterol in thyroid disease.

*Recurrent Hyperthyroidism.*—Ten of the group of patients with exophthalmic goiter were known to be toxic again on the completion of this study. In these cases, data were obtained which showed a lowering of the blood cholesterol on recurrence or a failure to rise if

hyperthyroidism persisted after operation. In a few cases, in spite of persistent mild toxicity, the value for cholesterol rose in conjunction with a gain in weight and a lowering of the basal metabolic rate.

#### COMMENT

The results so far set forth indicate a reciprocal relationship, based on average values, between the basal metabolic rate and the blood cholesterol value during fasting. It has been stated<sup>1</sup> that there is no relationship between the level of the blood cholesterol and the basal metabolic rate in people apparently not suffering from thyroid disturbance. This appears to be true at first glance, but it must not be forgotten that the "normal" basal metabolic rate ( $-10$  to  $+10$ ) is based on averages, and that normal persons may have rates varying 40 points, from minus 20 per cent to plus 20 per cent. The same fact is true for the level of the blood cholesterol. If thyroid extract is administered to a person in whom these two factors can be determined, or the output of the thyroid is diminished by surgical intervention, roentgen treatment or infection, the change in these two variants will tend to be reciprocal. Naturally, other causes which affect cholesterol, such as infection, nephrosis and diabetes, must be excluded.

The effect of preoperative treatment on the blood cholesterol in toxic adenomatous goiter and in exophthalmic goiter was found to be approximately the same. This finding could lead to further discussion as to the effect of iodine in these two clinical types of goiter and as to whether or not there is any fundamental difference between them. As only eight cases were studied preoperatively, a conclusion in this regard would not be trustworthy.

There appears to be a greater variation in the blood cholesterol after operation in exophthalmic goiter than in toxic adenomatous goiter. Assuming that in a case of toxic adenomatous goiter the hyperfunctioning part is confined to the adenomas, removal of these growths should leave a relatively greater portion of normally functioning tissue than in exophthalmic goiter. Surgical treatment of exophthalmic goiter, it seems to me, resembles a tailoring process in which the best results are obtained when the surgeon, through experience in handling the different types of glands in that disease, is able to trim the thyroid to fit individual needs. When he leaves behind a tissue of varying quality and quantity, a good fit, so to speak, is a difficult problem. The size of the remnants left behind in some cases may be several or more times larger than in others. Hence one might expect to find

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1. Grabfield, G. P., and Campbell, A. G.: A Note on the Relation Between Blood Cholesterol and Basal Metabolic Rate, *New England J. Med.* **205**:1148 (Dec. 10) 1931.

patients left with all degrees of thyroid function; in the majority the function is normal or so nearly normal as to escape either the patient's or the physician's attention, and in a few there is still overfunctioning or underfunctioning to an obvious degree.

Is the blood cholesterol of any value in the diagnosis of hyperthyroidism? I think that only general conclusions are warranted in this respect. In part I it was shown that the more severe cases showed the lowest cholesterol levels. If the cholesterol value is below 100 mg. per hundred cubic centimeters in toxic goiter, without acute infection, the patient is almost certainly very toxic. If the cholesterol value is over 180 mg. per hundred cubic centimeters, with or without the previous administration of iodine, there is only slight or moderate toxicity. The determination of the cholesterol content of the blood appears to be of little value in borderline cases, except that if the determination shows a level of over 200 mg. per hundred cubic centimeters, the condition is not likely to be hyperthyroidism unless there has been a complete remission due to the administration of iodine. There are instances of patients with hypertension, goiter, and basal metabolic rates reaching as high as plus 60 or plus 70 in which the clinical evidence is decidedly against hyperthyroidism. In such cases, cholesterol values of 160 or more are usually found, a finding which is out of proportion to the basal metabolic rate, and which serves, I believe, as a definite indication that the thyroid is not the cause of the elevated metabolic rate. On the other hand, I feel that the cholesterol content of the blood is of distinct importance in the diagnosis of hypothyroidism; this will be taken up in part III of this study.

#### CONCLUSIONS

1. The blood cholesterol is low in toxic thyroid states, and is brought to a normal level partly by preoperative treatment but chiefly by subtotal thyroidectomy.
2. The reciprocal relationship between the average elevation of the basal metabolic rate and the average lowering of the blood cholesterol level in toxic goiter, as was shown in part I of this study, is further confirmed by the results of treatment presented in this paper.
3. There appears to be little difference between the change in the blood cholesterol values in exophthalmic goiter and that in toxic adenomatous goiter as the result of treatment.
4. The blood cholesterol in nontoxic adenoma or adenomatous goiter undergoes little or no change as the result of removal of the growth.
5. The blood cholesterol determination is of distinct but limited value in the diagnosis of hyperthyroidism.

# PHYSICAL CHARACTERISTICS OF RESIDUES FROM THE SMALL INTESTINE

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AND

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The opportunity of observing a patient with an ileostomy led to the following studies on the consistency, color, water and nitrogen content and time of appearance of the material from the small intestine. The reaction of the ileal contents, degree of absorption of the various products of digestion and the exchange of minerals at this level are questions which have been inadequately studied. Reports of work on patients and animals with fistulas, at various points or with varying lengths of the colon excised, have been published from time to time.

The best of the early work is probably that of Heile,<sup>1</sup> who used dogs with ileocecal fistulas. He found that absorption of nitrogen was nearly complete, i. e., 98 per cent on a moderate intake of meat and 88 per cent with great overfeeding. The absorption of carbohydrates fed in the form of rice and sugar was also complete, as was the absorption of milk except when fed in very large amounts. The reaction of the residues was alkaline to litmus; in fact, sufficient alkali was present to neutralize small portions of dilute sulphuric acid. To some extent the alkalinity varied with the diet, being greatest with meat and least with fat. It increased up to the fourth hour after the feeding of meats, but was at its height in the first hour in the case of carbohydrates and fats. On the other hand, Heile found that the absorbing ability of the colon was very small in both man and dogs. Neither the native proteins nor the partially digested proteins, given in the form of enemas, were absorbed, while sugar was utilized to about 20 per cent and water 50 per cent.

Graham and Emery,<sup>2</sup> working on dogs, determined the reaction of the intestinal contents at different levels, particularly after periods of feeding with all meat, all bread and all lard. In these experiments the dogs were killed twenty-four hours after feeding, portions of the intes-

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Nitrogen content and reaction were also studied.

From the Department of Internal Medicine, State University of Iowa.

1. Heile, B.: Experimentelle Beobachtungen über die Resorption im Dünn- und Dickdarm, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **14**:474, 1905.

2. Graham, W. R., and Emery, E. S., Jr.: The Reaction of the Intestinal Contents of Dogs Fed on Different Diets, *J. Lab. & Clin. Med.* **13**:1097, 1928.

tines tied off, and the reaction of the contents determined colorimetrically. The type of previous feeding had no effect on the reaction, which was slightly acid in the duodenum and jejunum ( $p_H$  6.2 to 6.5), less acid to slightly alkaline in the ileum, and acid again in the cecum. Material from a fistula of the ileum gave a slightly alkaline reaction.

Beuttenmüller,<sup>3</sup> observing a case of ulcerative colitis with a cecal fistula, concluded that the ordinary meal stays in the small intestine two or three hours, a water-poor diet from four to five hours and a fluid diet from one to one and a half hours.

Alvarez and his associates<sup>4</sup> have reported a great deal of work as to the effect of different types of food on the physical properties of the residue collected through the rectum in which an ileorectal anastomosis had been made. They published two series of experiments, a year apart, in which results differed slightly, probably owing to a hypertrophy of the rectum, which was especially marked in one dog. In general, they concluded that the fasting residue was fecal in odor, dark brown in color, of the consistency of thin mush and neutral to litmus. The residue of such foods as liver, gelatin and broth resembled the stools of fasting dogs in color, odor, consistency and reaction. That of carbohydrate foods, such as rice, bread, bananas and sugar, was light canary-yellow and thicker in consistency than the stools of the fasting dogs. The protein foods appeared in four and one-half hours, while the carbohydrates and fats, with the exception of rice and lard, came through more rapidly. The fruits, liquid foods, water and sugar appeared in from fifteen to forty-five minutes. Milk was intermediate, requiring three hours. The percentage relation between the moist weight of the food and the moist weight of the residue was used as an index of digestibility. On this basis, gelatin, sucrose, dextrose, karo corn syrup, meat, rice and cottage cheese showed the smallest percentage of moist residue and therefore the highest efficiency of digestion, whereas fruits, potatoes, bread, raw egg albumin, milk and lactose showed the largest percentage moist residue or the poorest efficiency of digestion. They stressed particularly the fact that raw egg albumin passed through the intestinal tract unchanged and that milk gave consistently very large residues. However, their figures show that small quantities of milk (255 Gm.) have an efficiency of digestion equivalent to rice or cottage cheese. This efficiency of digestion is markedly decreased when the quantity of milk is doubled. The residues had a water content ranging from 83 to 90 per cent. Combinations of certain

3. Beuttenmüller, Helen: Beobachtungen an einer Zockalfistel, München. med. Wchnschr. 1:743, 1920.

4. Hosoi, K.; Alvarez, Walter C., and Mann, Frank C.: Intestinal Absorption: A Search for a Low Residue Diet, Arch. Int. Med. 41:112 (Jan.) 1928.

foods, such as bread and milk and raw egg and milk, improved digestion of both. Lactose proved to be a laxative. Lactose, cheese and lard interfered with digestion the following day. Meat was better digested when fed in lumps than when ground. Foods taken in one large amount were better utilized than when taken in divided portions.

In later work, Alvarez and his co-workers<sup>5</sup> added two dogs with ileal fistulas. In these animals, they found that the taking of food led to the extrusion of material from the fistula with the appearance of the first residues from a given meal in two and one-half hours. Liquids appeared somewhat sooner.

#### EXPERIMENTAL PROCEDURE

A 19 year old girl, who had had ulcerative colitis of two years' duration and on whom an ileostomy had been done as a therapeutic procedure, was used as the experimental subject. The diagnosis had been established as the result of abundant clinical, roentgen and laboratory evidence, and the patient had fully recovered her health prior to the investigative period.

Collection of material was made in an ileostomy bag which fitted tightly to the opening in the abdomen, the skin being protected by a thick coat of hydrous wool fat. The patient had breakfast at 7 a. m., and the same breakfast was fed on three successive days. Following the breakfasts of the first series, lunch was given at about 12 noon. This was exactly duplicated in a second control series. The third series was similar to the preceding two except that lunch was delayed until all the residue had been excreted from the experimental meal. A fourth series was run in which the breakfast was divided into three feedings an hour apart. Dinner was eaten at 5 p. m. The last of the residue from the dinner meal appeared at the terminal ileum about 5 a. m. Only clear bile-stained fluid was collected at the terminal ileum after this time. The experimental breakfasts were marked off by means of 1 ounce of grapejuice, given at the beginning of lunch. The marking was definite, and proved much more satisfactory than such material as carmine or charcoal. (The daily breakfasts are given in table 1.)

#### METHODS OF ANALYSIS

The water content of the moist material was determined by weighing the contents of the ileostomy bag and then drying this material to a constant weight. The reaction of the residue was obtained by electrometric titration.<sup>6</sup> Quinhydrone on gold was used in conjunction with a saturated mild mercurous chloride cell. The nitrogen content was ascertained by the Kjeldahl<sup>7</sup> method on 0.5 Gm. of dried pulverized sample. Duplicates were run on all samples.

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5. Childrey, J. H.; Alvarez, W. C., and Mann, F. C.: Digestion Efficiency with Various Foods and Under Various Conditions, *Arch. Int. Med.* **46**:361 (Sept.) 1930.

6. Clark, W. M.: *The Determination of Hydrogen Ions*, Baltimore, Williams & Wilkins Company, 1928, chap. 19.

7. Hawk, P. B., and Bergeim, O.: *Practical Physiological Chemistry*, Philadelphia, P. Blakiston's Son & Co., 1926, p. 711.

## RESULTS

*Color and Consistency* (table 2).—The residues collected by way of the ileofistula varied in color from bright yellow with milk and milk products to a dark green with meat. At no time was a fecal odor noticed. The consistency varied from a curdy, nonhomogeneous, thin

TABLE 1.—*Experimental Breakfasts*

Breakfast	Weight	Dry Weight	Nitrogen
Milk.....	724	94.2	3.02
	580	75.4	3.05
Bread.....	90	.....	.....
Milk.....	630	140.0	4.60
Bread.....	100	.....	.....
Water.....	167	65.0	1.48
Bread.....	90	.....	.....
Water.....	450	58.5	1.34
Bread.....	90	.....	.....
Butter.....	60	.....	.....
Water.....	167	111.9	1.43
Bread.....	90	.....	.....
Orange.....	100	.....	.....
Water.....	167	98.3	1.50
Milk.....	600	.....	.....
Orange.....	100	91.1	3.5
Meat.....	175	.....	.....
Water.....	167	62.3	3.2
Cream.....	600	156.0	2.0
Bread.....	90	.....	.....
Jelly.....	90	115.6	.....
Candy.....	10	.....	1.04
Water.....	167	.....	.....
Normal breakfast.....	518	213.0	2.91

TABLE 2.—*Color and Consistency*

Food	Color	Consistency
Milk.....	Light bright yellow	Curded
Milk and orange.....	Light bright yellow	Curded, orange particles
Cream.....	Bright yellow	Curded
Milk and bread.....	Yellow-green	Thin mush
Bread.....	Yellow-brown	Smooth, thin mush
Bread and butter.....	Light yellow-brown	Curded
Bread and orange.....	Yellow-brown	Semisolid, foamy
Balanced diet.....	Brown	Curded
Bread, jelly and candy.....	Dark green	Fluid, smooth
Meat.....	Black-green	Slightly viscous
		Smooth thin mush
Milk, divided into 3 feedings.....	Yellow-green	Very fine curd
Bread and milk, divided feedings.....	Yellow-green	Smooth, thin mush

gruel-like material with milk, to a smooth, thin gruel with meat. When the food was given at hourly intervals, the consistency was smoother. Feeding of milk at hourly intervals produced a residue of fewer curds and of a less bright yellow color.

*Percentage Relation of Dry Residues.* (table 3).—The percentage relation between the dry weight of the residues and the weight of material ingested varied slightly with the different foods. Some of this

TABLE 3.—*Weight of Residues*

Food	Period I				Period II			Period III		
	Moist Weight, of Food	Moist Weight, Gm.	Dry Weight, Gm.	Per Cent of Food Ex-creted	Moist Weight, Gm.	Dry Weight, Gm.	Per Cent of Food Ex-creted	Moist Weight, Gm.	Dry Weight, Gm.	Per Cent of Food Ex-creted
Milk.....	724.0	171.5	9.5819	1.3	152.0	6.0682	2.0	191.3	7.4821	2.6
	580.0	149.6	10.7688	1.8	106.2	7.1670	1.8	181.0	9.9329	3.1
Milk.....	721.3	158.1	10.9868	1.5	.....	.....	...	.....	.....	...
Bread.....	723.0	193.6	11.7245	1.6	.....	.....	...	.....	.....	...
	690.0	143.6	11.7367	1.7	131.0	7.4299	1.0	220.0	11.0880	1.6
Bread.....	267.0	99.0	4.5478	1.7	.....	.....	...	.....	.....	...
Water.....	267.0	154.0	6.7953	2.5	106.5	6.3851	2.3	151.0	6.9042	2.7
	246.0	145.0	6.8579	2.7	.....	.....	...	.....	.....	...
Bread, 450 cc.....	540.0	146.5	7.3263	1.3	116.4	5.0820	0.9	192.6	8.2500	1.5
Water.....	520.0	121.7	7.5555	1.4	118.5	5.5347	1.0	203.6	10.1042	1.9
Milk.....	700.0	200.9	9.2259	1.3	112.0	6.3383	0.9	.....	.....	...
Orange.....	700.0	181.2	7.5434	1.0	202.6	8.8025	1.2	.....	.....	...
	700.0	198.0	12.0237	1.7	218.5	8.6583	1.2	.....	.....	...
Meat.....	292.0	101.6	3.3639	1.1	32.0	1.6137	0.5	141.0	4.7760	1.6
	342.0	127.6	5.2161	1.5	141.0	2.6829	0.7	134.0	3.1784	0.9
	342.0	141.9	3.7746	...	.....	.....	...	.....	.....	...
Balanced.....	498.0	114.2	6.2409	1.2	.....	.....	...	.....	.....	...
	498.0	175.0	7.7527	1.5	.....	.....	...	.....	.....	...
	408.0	165.7	6.2810	1.5	.....	.....	...	.....	.....	...
	408.0	199.8	8.6412	2.1	.....	.....	...	.....	.....	...
Bread.....	321.0	218.0	5.8528	1.8	121.6	7.2585	2.2	101.4	7.3773	2.2
Jelly.....	327.0	182.3	6.9122	2.1	186.7	8.1065	2.4	150.0	6.8162	2.0
Candy.....	.....	.....	.....	...	.....	.....	...	.....	.....	...
Cream.....	600.0	157.0	6.8931	1.1	111.0	5.1590	0.8	282.0	11.5001	1.9
	415.0	97.9	5.2600	1.2	134.0	6.5415	1.5	183.5	9.1562	2.2

TABLE 4.—*Water Content of Residues*

Food	Weight, Gm.	Period I, per Cent of Water	Period II, per Cent of Water	Period III, per Cent of Water
Milk.....	724	....	96.1	96.1
Milk.....	724	94.4	96.1	96.6
Milk.....	580	92.2	93.9	94.6
Bread and milk.....	721	93.1	93.5	95.0
	721	93.9	93.7	94.7
	721	....	94.9	....
Bread and water.....	267	95.4	94.1	95.8
Bread and water.....	...	95.6	....	95.5
Bread and water.....	...	95.3	....	95.1
Bread and water.....	540	95.1	95.7	....
Bread and water.....	520	93.0	95.4	....
Bread.....	...	94.4	95.1	....
Butter.....	317	93.4	94.3	....
Water.....	...	93.7	96.0	....
Meat.....	125	96.7	....	....
	175	95.9	95.0	96.7
	175	97.3	97.9	96.1
	175	....	....	95.8
	175	....	....	97.7
	175	....	....	97.6
	...	....	....	95.7
Bread and jelly.....	321	97.4	94.1	....
Candy.....	...	96.3	95.7	....
	...	....	93.8	....
Cream.....	600	95.6	95.4	97.0
	415	94.6	95.2	95.0
Average of all determinations, 94.8%				



TABLE 5.—*Time of Appearance of Residues*

Food	Period I			
	Breakfast	First Residue	Marker Appeared	Lunch
1. Milk.....	7:00	9:30	1:40	12:00
Milk.....	7:00	9:20	2:00	1:10
2. Milk.....	7:10	9:00		
Bread.....	7:10	8:25	1:30	12:00
Bread.....	7:15	8:25	1:30	12:20
Bread.....	....	....	2:15	12:00
3. Bread				
Water.....	7:10	10:40	1:30	12:00
Water.....	7:00	10:15	1:15	12:00
Water.....	7:00	10:40	1:20	12:00
4. Bread				
Water.....	7:00	10:00	1:10	12:00
Water.....	7:00	10:00	12:55	12:00
5. Bread.....	7:00	8:30	12:55	12:00
Butter.....	7:00	8:30	1:10	12:00
Water.....	7:00	9:50	1:00	12:00
6. Bread.....	7:00	8:30	1:00	12:00
Orange.....	7:00	8:30	1:00	12:00
	7:00	8:30	1:00	12:00
7. Bread.....	7:00	8:30	1:30-2:10	1:00-2:00
Butter.....	7:00	8:30	3:15	2:00
Orange.....	7:00	8:30	2:45	2:00
8. Milk.....	7:00	10:30	1:00	12:00
Orange.....	7:00	9:30	1:10	
	7:00	9:45	1:15	
9. Meat.....	7:00	11:45	1:00	12:00
	7:00	11:35	1:30	12:00
	7:00	11:15	1:35	12:35
10. Balanced breakfast.....	7:00	9:00	1:30	12:00
	7:00	9:00	1:25	12:00
	7:00	9:00	1:05	
			1:00	
11. Bread.....	7:00	9:15	1:10	
Jelly.....	7:00	8:45	1:00	12:00
Candy				
12. Cream 40%.....	7:00	8:15	12:50	12:00
	7:00	8:30	1:10	12:00
Period II				
Milk.....	7:15	8:35	1:45	11:55
Milk.....	7:10	8:30	1:50	11:55
Milk.....	7:00	8:55	2:00	11:55
Bread and milk.....	7:00	8:30	1:15	11:50
Bread and milk.....	7:00	8:35	1:45	11:55
Bread and milk.....	7:00	8:35	1:45	11:50
Bread and water.....	7:00	10:55	1:15	11:50
Bread and water.....	6:45	9:45	1:10	11:45
Bread and water.....	6:45	10:15	1:00	11:45
Bread, butter and water.....	7:00	9:15	12:30	11:45
Bread, butter and water.....	7:00	9:15	12:35	11:45
Bread, butter and water.....	7:00	9:00	12:35	11:55
Meat.....	7:00	11:45	1:00	12:00
Meat.....	7:00	11:30	12:50	11:55
Cream.....	7:00	8:30	12:35	11:45
	7:00	8:30	12:35	11:50
Bread.....	7:00	9:30	1:15	11:50
Candy and jelly.....	7:00	9:15	1:05	11:50
Candy and jelly.....	7:00	9:15	1:00	11:55
Period III—Delayed Lunch				
Milk.....	7:00	9:35	4:45	5:00
Milk.....	7:00	8:00	4:45	5:10
Milk.....	7:00	8:30	5:00	5:15
Bread and milk.....	7:00	8:45	4:45	5:10
Bread and milk.....	7:00	8:45	4:50	5:00
Bread and water.....	7:00	9:45	4:45	5:00
Bread and water.....	7:00	10:00	4:45	5:00
Bread and water.....	7:00	9:45	5:05	5:15
Meat.....	7:00	10:30	5:10	5:15
Meat.....	7:00	10:05	5:05	5:15
Meat.....	7:00	11:15	5:05	5:15
Meat.....	7:00	11:15	5:00	5:10
Cream.....	7:00	8:30	5:10	5:30
Cream.....	7:00	8:30	5:05	5:15

variation was due, no doubt, to the difference in the amounts of the nonabsorbable constituents of the material fed. This variation was from 1 to 3 per cent and, considering the difference in the amounts and types of food fed, was not remarkable. The weights of the residues obtained in the third period, when the 12 o'clock feeding was omitted, were similar to those in periods I and II.

*Water Content of Residues* (table 4).—Though the consistency of the different residues varied according to the food fed, the actual water content was found to be remarkably constant. The lowest figure was 92.2 per cent and the highest 97.7 per cent. Most of the residues had a water content of about 94 per cent.

*Time of Appearance of Residues* (table 5).—The time of appearance of the residue after feeding bore little relation to the amount of the feeding, to the consistency or to the water content. Cream appeared

TABLE 6.—*Reaction of the Residues*

	$p_H$		$p_H$		$p_H$
Milk.....	6.84 7.58	Bread and butter.....	7.21 6.88 6.89	Meat.....	7.73 7.52 7.56
Milk and bread.....	7.17 7.02 7.19	Bread and orange.....	6.55 6.67 7.11	Balanced breakfast....	7.11 7.08 6.58
Bread and water.....	7.16 6.41 6.76	Milk and orange.....	7.32 6.66 6.90	Bread, jelly, candy....	6.93 6.46
Bread and water.....	7.23			40% cream.....	7.46

the earliest, 8:15 a. m., and meat the latest, 11:30. The residue of bread and water was extruded after that of bread and milk and bread and butter. The completion time was influenced by the second meal. In general, the breakfast marker appeared from one and one-quarter to one and one-half hours after lunch, whether this was given at 12, 1 or 2 o'clock. In period III, when no meal was given at noon, the marker appeared between 4:45 p. m. and 5 p. m.

*Reaction* (table 6).—For the most part, the reaction of the residues varied around the neutral point. The lowest or most acid values ( $p_H$  6.4) were with bread, jelly and candy, and with bread and water. The highest or most alkaline reaction was  $p_H$  7.7 with meat.

*Nitrogen Content of the Residues* (table 7).—Nitrogen was excreted in small amounts, independent for the most part of the amount of nitrogen in the diet. Table 7 shows a variation of 0.09 to 0.45 Gm. nitrogen found in the residues. However, most of the nitrogen weights were from 0.2 to 0.3 Gm. The percentage of nitrogen in the residues varied from 1.6 to 7.8. The highest percentage values were obtained from the meat residues, though the actual amount of nitrogen

excreted following these feedings was no larger than with other foods. Holding the food longer in the body, or giving the food in small frequent feedings did not influence the nitrogen excretion.

*Effect of Small Feedings* (table 8).—Milk, milk and bread, and meat were given in three feedings instead of one. There was an appre-

TABLE 7.—*Nitrogen Excretion*

Food	Weight, Gm.	Weight of Nitrogen Excreted in Dry Residues, Gm.			Per Cent of Nitrogen in Dry Residues		
		Period I	Period II	Period III	Period I	Period II	Period III
Milk.....	724	0.3150	0.1435	0.2774	3.2	1.9	5.9
	724	.....	0.1112	0.2902	...	1.8	2.6
	580	0.2487	0.1211	0.4227	2.3	1.6	4.2
Milk and bread.....	600	0.3390	0.3005	0.2483	3.0	3.3	2.2
	90	0.4168	0.2570	0.4547	3.5	3.3	3.8
		0.3170	0.2302	.....	3.0	3.1	
Bread and water...	90	0.1680	0.2509	0.2829	3.6	3.9	2.8
	167	0.2030	.....	0.3164	2.9	...	3.8
		0.2260	.....	0.2551	3.2	...	3.6
Bread and water...	90	0.2388	0.1367	.....	3.2	2.9	
	540	0.2274	0.1892	.....	3.0	3.6	
Meat.....	125	0.1958	0.1258	0.3119	5.8	7.8	6.5
	175	0.3607	0.1016	0.4000	6.9	3.7	7.4
	175	0.2174	.....	0.2449	5.7	...	5.7
	175	.....	.....	0.2015	...	...	6.3
	175	.....	.....	0.2018	...	...	4.2
	175	.....	.....	0.3261	...	...	4.4
Bread, jelly, candy	90	0.2917	0.2410	.....	4.2	3.2	
	60	.....	0.2902	.....	...	3.5	
	10	.....	0.1888	.....	...	3.4	
Cream.....	600	0.1364	0.0949	0.1948	1.9	1.8	1.6
		0.1421	0.1583	0.2041	2.7	2.4	2.2

TABLE 8.—*Residues from Divided Feedings*

Food	Weight, Gm.	Moist Weight of Residues, Gm.	Dry Weight of Residues, Gm.	Per Cent of Water	Weight of Nitrogen, Gm.	Per Cent of Nitrogen
Milk divided into 3 feedings....	724	73.0	4.2715	94.2	0.1750	4.1
	580	115.9	6.4735	94.5	0.2573	4.9
	580	80.4	4.8748	93.9	0.2183	4.4
Milk and bread divided.....	540	115.3	8.7498	92.5	0.2658	5.0
Meat divided.....	175	90.8	4.8800	96.1	0.2195	4.7

ciable decrease in the weight of the residues and a change in the consistency and color, but the water and nitrogen contents were unchanged.

#### SUMMARY

The residues obtained from an ileal fistula varied in consistency and color with the type of food. Milk and milk products gave a curdled yellow mixture; bread and jelly, a dark brown, smooth, thin gruel, and meat, a very dark green, smooth, thin gruel. No fecal odor was noticed at any time. The water content was remarkably constant for all kinds of food (92 to 97 per cent), including a normal breakfast. The nitro-

gen content was approximately constant and was independent of the type or time of feeding. The weight of the residue, either moist or dry, varied with the kinds of food and only slightly with the amount fed. In general, the feeding of milk and milk products resulted in the highest dry residues. The residues appeared from the ileal fistula at one and one-fourth to four and one-half hours after breakfast. Cream appeared from one to one and a half hours after the second feeding. When no second meal was fed, the last of the breakfast residue appeared between 4 p. m. and 5 p. m. Small frequent feedings, particularly of milk, changed the consistency of the residue and the dry and moist weights, but did not affect either the water or the nitrogen contents.

# INFLUENCE OF SODIUM NITRITE ON THE CARDIOVASCULAR SYSTEM AND ON RENAL ACTIVITY

IN HEALTH, IN ARTERIAL HYPERTENSION AND IN RENAL DISEASE

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The nitrites are chiefly used in the treatment of angina pectoris and related angiospastic disorders; nevertheless they have been and are being widely employed therapeutically for patients with arterial hypertension.

In the present study it was desired to investigate the clinical effects of sodium nitrite on normal persons, on patients with primary arterial hypertension, with or without involvement of the kidneys, and on patients with certain other renal disorders. In addition to observations of the clinical state of the patient, cardiac rate and arterial blood pressure, determinations of the cardiac output were performed; and in particular, investigations were undertaken as to the nature of changes in the renal function as measured by the volume of urine, the urea clearance test of Van Slyke and the creatinine filtrate method of Rehberg. In view of the fact that the nitrites produce vasodilatation and often lower the arterial blood pressure, the effect on renal function through these cardiovascular changes was of particular interest.

## MATERIAL AND METHODS

The ten subjects chosen as "normal" were either healthy physicians and medical students or hospital patients convalescent from disorders which had no effect on the cardiovascular system. In all of the twenty-nine patients with arterial hypertension the condition was of the so-called "essential" type, and none had clinical symptoms of renal failure at the time the tests were made. As will be seen, however, the sensitive renal function tests indicated that they suffered to a varying extent from loss of renal reserve. The five cases of glomerular nephritis ranged in severity from mild to very marked. Nine persons in whom unilateral nephrectomy had been performed a year or more prior to this study were also investigated.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Six of these were clinically well and had renal functions which were normal or nearly so. The remaining three suffered from complications; two had pyonephrosis, involving the remaining kidney, and one hypertension.

Measurements of blood pressure were performed with a mercury sphygmomanometer, and in some instances were also recorded graphically with a Tycos recording sphygmomanometer. The estimations of the cardiac minute volume outputs were made according to the Fick principle by the method of Field, Bock, Gildea and Lathrop.<sup>1</sup> The technic of Möller, McIntosh and Van Slyke<sup>2</sup> was employed to determine the urea clearance test. In all instances in the accompanying tables the results are expressed as "maximum" clearance, according to the formula,

$$\frac{\text{concentration urine urea}}{\text{concentration blood urea}} \times \text{urine volume per minute}$$

although in certain instances the output of urine fell below 2 cc. per minute, and under such conditions it is known that the urea clearance diminishes. The determination of urea in blood and urine was carried out by the gasometric method.<sup>3</sup> Rehberg's technic for calculating the degree of glomerular filtration by means of creatinine was used,<sup>4</sup> the formula employed being the same as that in calculating the urea clearance, with the substitution of creatinine for urea. The estimation of blood and urine creatinine was performed by the method of Folin,<sup>5</sup> using purified picric acid. For a discussion of the significance of the results obtained in estimating renal function by the urea or creatinine clearance procedure, reference is made to our previous study.<sup>6</sup> In summary, it is believed that both of these procedures are gages of the extent of glomerular filtration and that the creatinine technic probably provides a close absolute index of this filtration. Under conditions of marked diuresis (2 cc. of urine per minute or more) the urea clearance is a relative index of filtration, but when the output of urine falls, increased back diffusion of urea through the tubular walls into the blood serves to lower the urea clearance as compared to the creatinine clearance values.

The creatinine and urea determinations were made on the same specimens of blood and urine, so that the results are comparable. At least 200 cc. of water was given to the subjects each hour during which the tests were carried out in order to provoke a marked diuresis.

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*Dosage of Nitrite.*—Sodium nitrite in tablet form was administered by mouth. The usual dose administered was from 3 to 5 grains (0.2 to 0.3 Gm.). In the studies on renal function 3 grains of sodium nitrite was administered in water about five minutes before the start of the period of urine collection. Half an hour later another 2 grains (0.13 Gm.) was given, unless the symptoms produced by the first dose were marked in degree. These doses are large therapeutic doses, and in a number of instances produced undesired effects.

#### EFFECTS OF SODIUM NITRITE

*Symptoms.*—There was no particular correlation between the symptoms produced and the size of the dose of sodium nitrite. Thus, in one subject 5 grains of sodium nitrite might produce no subjective sensations whatever, while in a second the same amount would cause severe symptoms. Moreover, there was no relationship between the symptoms and the degree of fall in blood pressure except in the cases in which the degree of depression of blood pressure or the intensity of symptoms was marked. The most common subjective sensation complained of was a throbbing headache. Other symptoms were weakness, giddiness and faintness, which in the most extreme cases verged on unconsciousness. Only nine of the fifty-three subjects experienced severe symptoms. Objectively, there was frequently some cyanosis of the extremities, and the peripheral palpable arteries occasionally appeared relaxed under the influence of the nitrite. This dilatation was confirmed by the graphic records, which showed increased amplitude of excursion. When symptoms of faintness, cyanosis, etc., occurred, they usually took place within thirty minutes after the ingestion of the nitrite, although on a few occasions the subject first noticed faintness and giddiness from one to two hours after the administration of the drug, when he rose from the reclining position. Headache occasionally persisted in mild form for several hours.

*Heart Rate* (tables 1, 2 and 3).—The response of the cardiac rate was not constant. Doses of from 1 to 2 grains (0.06 to 0.13 Gm.) usually produced an insignificant rise or none. With doses of from 3 to 5 grains the average increase in the pulse rate for both normal persons and patients with hypertension was about 8 beats per minute, although in a few instances increases of from 20 to 40 beats were noted. This rise ordinarily lasted less than thirty minutes; in rare instances it persisted for an hour. No relationship was found between the cardiac rate and other symptoms and objective changes.

*Arterial Blood Pressure* (tables 1, 2 and 3).—The changes in the normal arterial blood pressure which were observed were similar in nature and extent to those noted by others who have studied the effect of sodium nitrite. The action of the drug on the blood pressure was manifest in from five to fifteen minutes after ingestion. The delay

TABLE 1.—The Effect of from One to Five Grains of Sodium Nitrite on the Heart Rate, Arterial Blood Pressure, Cardiac Output and Basal Metabolic Rate in Normal Subjects and in Patients with Hypertension and with Glomerulonephritis

Sub- ject	Age, Yrs.	Heart Rate		Arterial Blood Pressure, Systolic/Diastolic, Mm. Hg			Cardiac Output per Minute, L.		Cardiac Output per Stroke, Cc.		Basal Metabolic Rate, per Cent		Dose, age, Grains	Symptoms				
		Be- fore	Nitrite	Difference	Under Sodium Nitrite		Be- fore	Nitrite	Be- fore	Nitrite	Be- fore	Nitrite						
					Maximum	Average												
															Before			
1	30	72	80	+ 8	113/ 70	83/ 45	100/ 55	-13/-15	6.4	6.9	+0.5	89	86	- 3	+ 3	- 6	Headache	
2	36	72	95	+23	113/ 73	96/ 56	100/ 58	-13/-15	6.1	5.8	-0.3	86	61	+37	+12	+25	None	
3	28	54	60	+ 6	95/ 40	80/ 40	50/ 45	-5/-15	4.6	4.6	0	85	77	- 8	- 1	0	None	
4	28	60	60	0	115/ 68	100/ 50	100/ 58	-15/-10	4.3	4.3	0	72	72	0	+ 2	- 1	Fatiguess	
5	40	64	70	+ 6	95/ 60	84/ 50	90/ 50	- 5/-10	6.7	6.2	-0.5	105	88	+ 7	+ 8	- 1	None	
Normal Subjects																		
Subjects with Hypertension																		
6	60	60	84	+24	250/120	172/ 80	195/110	-55/-10	...	...	.....	..	..	...	...	...	3	Slight headache
	60	84	100	+24	270/136	203/120	217/125	-53/-11	...	...	.....	..	..	...	...	...	3	Slight palpitation
	60	100	100	+40	260/120	190/100	210/105	-50/-15	5.6	5.4	-0.2	93	54	+ 1	+ 1	+ 1	5	Slight headache
7	48	60	85	+25	260/125	197/105	200/110	-60/-15	...	...	.....	..	..	...	...	...	5	None
8	72	72	72	0	235/125	185/100	195/110	-40/-15	3.4	3.1	-0.3	47	43	- 3	+ 2	- 5	3	None
9	55	70	70	0	189/100	130/ 75	135/ 75	-54/-25	7.6	5.1	-2.5	169	73	-36	+11	-12	3	None
10	59	72	80	+ 8	200/ 95	145/ 70	160/ 80	-40/-15	4.0	3.4	-0.6	64	50	+ 2	+ 5	- 3	3	Headache
11	55	76	90	+14	220/120	168/ 90	180/100	-40/-20	4.2	4.1	-0.1	58	51	- 9	+18	- 7	3	Very faint und pale
12	49	80	95	+15	230/120	165/ 75	175/ 95	-65/-23	...	...	.....	..	..	...	...	...	3	None
13	65	76	76	0	210/105	152/100	160/100	-50/-5	...	...	.....	..	..	...	...	...	3	None
14	50	88	88	0	180/110	144/ 95	150/100	-30/-10	...	...	.....	..	..	...	...	...	1	None
15	49	94	90	- 4	275/138	232/130	230/132	-43/-6	...	...	.....	..	..	...	...	...	1	None
16	52	80	80	0	236/133	202/122	228/130	-8/-8	...	...	.....	..	..	...	...	...	1	Slight flush
	80	80	80	0	224/130	206/126	215/128	-9/-2	...	...	.....	..	..	...	...	...	2	None
17	24	94	96	+ 2	218/130	194/116	200/120	-18/-10	...	...	.....	..	..	...	...	...	1	None
	96	100	100	+ 4	174/122	158/118	162/120	-12/-2	...	...	.....	..	..	...	...	...	2	None
18	65	76	80	+ 4	174/124	156/116	160/120	-14/-4	...	...	.....	..	..	...	...	...	1	None
					213/120	203/110	210/110	- 3/-10	...	...	.....	..	..	...	...	...	2	None
									...	...	.....	..	..	...	...	...	3	None
Subjects with Glomerulonephritis																		
19	25	80	90	+10	147/105	130/ 80	130/ 85	-17/-20	...	...	.....	..	..	...	...	...	2	Fainted



and variation in the speed with which it acted were probably due to individual differences in the rapidity of absorption from the alimentary canal.

In normal persons when a fall in blood pressure of marked degree occurred, it was occasionally transitory, but usually persisted for about thirty minutes; some lowering of the pressure generally lasted for from one to two hours. In the normal subjects the blood pressure sometimes was not altered, but at times was found decreased by 34 mm. of mercury systolic and 15 mm. diastolic. The average decrease was 12 mm. systolic and 10 mm. diastolic.

In the patients suffering from arterial hypertension the decreased blood pressure tended to persist for a somewhat longer period than in normal persons, and usually lasted about two hours. In a few cases the blood pressure had not entirely regained its former level five hours after the ingestion of the drug, but since the level of the blood pressure in hypertension is notoriously subject to wide fluctuations, it would be unwarranted to ascribe this effect definitely to the nitrite. We have demonstrated<sup>7</sup> that the return of dilated arterioles to a normal state may be independent of the persistence of action of the dilator chemical substance.

The absolute extent of the drop in the pressure in these hypertensive persons was greater than in the control subjects and averaged 35 mm. of mercury systolic and 20 mm. diastolic. However, the percentage decrease was of the same order of magnitude in the two groups. The systolic pressure in the patients with hypertension was almost always reduced to a greater extent than the diastolic. In a few instances extreme lowering of the blood pressure occurred, the pressure in one case dropping from 240 systolic and 130 diastolic to 80 systolic and 70 diastolic. Such dramatic reduction was usually associated with pronounced symptoms, but this by no means invariably occurred. In several cases the pressure fell between 40 and 50 mm. of mercury without the subject experiencing any sensations whatsoever. In two cases the subjects, one normal and the other with chronic nephritis, became faint and cyanotic although the blood pressure changed only from 115 systolic and 68 diastolic to 100 systolic and 50 diastolic and from 147 systolic and 105 diastolic to 130 systolic and 80 diastolic respectively.

*Cardiac Output* (table 1).—In five normal persons and in an equal number of patients with hypertension, estimations of the cardiac output were performed under basal conditions, both before the administration

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7. Ellis, L. B., and Weiss, Soma: A Study of the Cardiovascular Responses in Man to the Intravenous and Intra-Arterial Injection of Acetylcholine, *J. Pharmacol. & Exper. Therap.* **44**:235, 1932.

TABLE 2.—The Effect of from Three to Five Grains of Sodium Nitrite on the Renal Function of Five Normal Persons and Seventeen Patients with Arterial Hypertension

Sub- ject	Age, Yrs.	Heart Rate		Arterial Blood Pressure, Systolic/Diastolic, Mm. Hg		Blood Urea Nitrogen, Mg. per 100 Cc.		Urea Clearance, Cc.		Creatinine Clearance, Cc.		Urine Volume per Minute, Cc.		Symptoms						
		Under Sodium Nitrite	Differ- ence	Before	Under Sodium Nitrite	Differ- ence	Be- fore	Under Sodium Nitrite	Differ- ence	Be- fore	Under Sodium Nitrite	Differ- ence	Be- fore		Under Sodium Nitrite	Differ- ence				
20	41	68	74	+ 6	104/ 70	104/ 70	0/0	12	13	34 70	68 0	0	120 129	123	0	0.4 2.2	7.4	+	5	Weak, dizzy
21	42	48	56	+ 8	114/ 70	80/ 60	-34/-10	15	14	61 67	64 0	0	135 162	130	0	2.4 7.0	6.4	0	5	None
22	22	72	86	+14	104/ 68	100/ 66	- 4/- 2	9	8	77 77	65 0	0	154 153	121	-	8.9 11.0	3.2	0	5	Headache
23	34	64	72	+ 8	100/ 62	86/ 50	-14/-12	11	..	64 96	72 0	0	162 180	117	-	1.5 4.3	2.0	0	5	Headache
24	31	61	70	+ 9	102/ 62	90/ 62	-12/ 0	7	7	112 119	86 -	-	172 136	132	0	4.7 8.0	2.5	0	5	None
Subjects with Hypertension																				
25	70	80	88	+ 8	216/100	164/100	-52/ 0	12	10	69 103	80 0	0	69 125	105	0	1.6 4.1	4.3	0	3	Cyanotic
26	60	..	..	....	158/102	135/ 85	-23/-17	17	16	58 47	56 0	0	157 93	127	0	0.8 0.9	1.5	0	5	None
27	39	..	..	....	220/120	170/100	-50/-20	..	..	59 48	45 0	0	98 86	104	0	10.2 5.8	7.2	0	2	None
28	66	..	..	....	185/ 88	152/ 75	-32/-13	15	14	54 48	47 0	0	118 112	102	0	4.8 6.3	4.3	0	5	None
29	55	..	..	....	204/120	175/105	-29/-15	27	25	19 36	20 0	0	40 ...	37	0	4.8 1.4	5.2	0	5	Weak, dizzy; fainted after one hour
30	42	72	80	+ 8	220/138	200/135	-20/- 3	12	12	47 26	51 0	0	...	...	..	4.1 3.0	5.0	0	5	None
31	61	96	104	+ 8	262/138	225/110	-37/-28	21	20	9 51	21 0	0	...	...	..	4.8 8.9	4.8	0	5	None
32	25	..	..	....	192/170	175/150	-17/-20	7	..	26 51	47 0	0	118 110	...	..	4.7 4.3	4.1	0	3	Slight headache
33	46	59	72	+13	144/ 94	132/ 90	-12/- 4	11	9	50 25	56 0	0	160 78	120	-	3.0 0.5	3.0	0	5	Headache; cyanosis
34	56	..	..	....	210/ 95	100/ 65	-110/-30	12	13	50 54	23 0	-	78 82	78	0	2.1 5.2	2.1	0	3	Pale, stuporous
35	45	90	102	+12	154/ 96	152/ 94	- 2/- 2	11	11	54 52	30 0	-	84 120	90	0	3.3 7.6	6.0	0	5	Slight headache
36	48	..	..	....	210/118	150/100	-60/-18	13	13	53 51	21 0	-	144 125	122	0	6.0 10.2	2.2	-	5	Slight headache; cyanosis
37	62	..	..	....	190/ 94	160/ 80	-30/-14	13	18	33 61	35 0	-	107 110	89	-	1.4 8.5	6.0	0	5	None
38	52	67	74	+ 7	210/105	170/ 90	-40/-15	10	9	60 51	42 0	-	122 ...	96	-	5.2 2.2	4.5	0	5	None
39	65	..	..	....	132/ 80	162/ 62	+10/-18	9	8	54 54	43 0	-	...	96	-	3.2 2.8	3.8	0	5	Headache
40	43	70	72	+ 2	176/ 98	138/ 86	-38/-12	7	7	84 67	31 0	-	118 142	71	-	6.2 9.2	1.3	-	5	Slight headache; very faint one hour later
27	39	..	..	....	240/130	80/ 70	-160/-60	17	16	59 48	7 0	-	98 86	7	-	10.2 5.8	0.4	-	5	Pale, cyanotic, stuporous

of sodium nitrite and during the height of its effect. In none of the normal persons was there observed any significant change in the cardiac minute volume output. In all five of the patients with hypertension there was a slight drop in the minute output under the action of the nitrite, but in three of these the decrease was insignificant. In two it amounted to 15 and 32 per cent respectively of the control output. In nine of the ten cases there was a drop in the stroke volume output of the heart, and in six of these it amounted to 15 per cent or more.

Previous studies in regard to the effect of nitrites on the blood flow are rather conflicting. Early work<sup>8</sup> suggested that amyl nitrite and nitroglycerine produced an increase in cardiac output. Lindhard<sup>9</sup> investigated the effect of the inhalation of amyl nitrite in four normal subjects. He found that when they reacted by a slight fall in blood pressure only, the blood flow increased in three and was unchanged in one. When a marked drop in blood pressure resulted, the output was increased in two, unchanged in one and decreased in one. Gaisböck and Jarisch<sup>10</sup> found that the cardiac output increased somewhat in two subjects following the intramuscular injection of from 0.01 to 0.02 Gm. of sodium nitrite, although the pulse rate and blood pressure remained unchanged.

In the present study of the cardiac output, the lowering of the blood pressure in normal subjects was slight or none occurred. The patients with hypertension all showed a significant drop in arterial pressure.

*Metabolism* (table 1).—In contrast to Meyer<sup>11</sup> who found a decrease in the oxygen consumption in six of seven patients to whom he administered nitroglycerine, we found alteration in the basal metabolism in only one of ten persons given sodium nitrite. In this "normal" person the metabolic rate increased from a level of plus 12 per cent to plus 37 per cent when he was under the influence of sodium nitrite, and was probably due to his apprehensive state.

*Renal Function*.—The effect of sodium nitrite on renal function was studied thirty-five times in thirty-four subjects. Five of these were normal persons; nine had one kidney only, sixteen suffered from arterial

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9. Lindhard, J.: Ueber das Minutenvolum des Herzens bei Ruhe und bei Muskelarbeit, Arch. f. d. ges. Physiol. **16**:233, 1915.

10. Gaisböck, F., and Jarisch, A.: Ueber den Einfluss von Natrium Nitrosum auf den Kreislauf, Wien. klin. Wchnschr. **40**:1540, 1927.

11. Meyer, J.: Contribution à l'étude du mode d'action des nitrites, Arch. d. mal. du cœur **19**:615, 1926.

TABLE 3.—*The Effect of from Three to Five Grains of Sodium Nitrite on the Renal Function of Four Patients with Glomerulonephritis and in Nine Persons with One Kidney*

Sub- ject	Age, Yrs.	Heart Rate		Arterial Blood Pressure, Systolic/Diastolic, Mm. Hg		Blood Urea Nitrogen, Mg. per 100 Cc.		Urea Clearance, Cc.		Creatinine Clearance, Cc.		Urine Volume per Minute, Cc.		Symptoms				
		Be- fore	Nitrite	Difference	Under Sodium Nitrite	Be- fore	Nitrite	Under Sodium Nitrite	Be- fore	Nitrite	Under Sodium Nitrite	Be- fore	Nitrite		Under Sodium Nitrite	Be- fore	Nitrite	Dose Grains
Subjects with Glomerulonephritis																		
41	24	80	88	+ 8	112/ 70	112/ 70	0/ 0	8	7	58	60	0	138	0	8.8	0	5	Drowsy
										56			137		8.5			
42	47	100	102	+ 2	195/110	168/ 95	-27/-15	119	116	5	5	0	2	0	2.5	0	5	None
										5			2		3.0			
43	19	..	..	....	140/ 92	120/ 80	-20/-12	11	11	36	14	--	95	--	1.7	0	4	None
										52			157		5.2			
44	37	80	88	+ 8	146/100	130/ 84	-16/-16	23	22	55	25	--	131	--	3.0	1.0	5	None
										49			116		2.8			
Subjects with One Kidney																		
45	43	64	70	+ 6	106/ 70	95/ 62	-11/- 8	12	11	72	71	0	76	0	4.5	0	5	None
										70			90		7.8			
46	52	70	82	+12	134/ 86	132/ 78	- 2/- 8	15	14	38	61	0	56	0	1.5	0	5	None
										33			57		1.6			
										116	49		104		9.6			
										52			61		4.7			
47	23	67	72	+ 5	106/ 70	102/ 72	- 4/+ 2	15	12	75	72	0	128	--	5.0	0	5	None
										53			113		8.5			
48	27	73	82	+ 9	110/ 76	92/ 64	-18/-12	18	19	55	27	--	70	--	0.7	0	3	Fainted
										51			65		0.6			
49	44	79	74	-- 5	195/120	170/100	-25/-20	18	18	39	22	--	66	--	6.5	0	5	None
										32			57		7.7			
50	50	85	82	-- 3	134/ 84	120/ 70	-14/-14	13	13	95	5	--	180	--	9.3	--	5	None
										92			163		7.8			
51	42	68	76	+ 8	100/ 64	84/ 66	-16/+ 2	13	10	72	60	--	113	--	9.4	1.2	5	None
										66			105		6.8			
52	40	72	75	+ 3	112/ 70	104/ 70	-- 8/ 0	5	5	81	54	--	142	--	10.0	--	5	None
										75			132		5.9			
53	47	70	82	+12	130/ 85	86/ 60	-44/-15	14	15	24	5	--	37	--	2.8	0.45	3	Cyanotic, weak
										20			34		2.5			

hypertension and four had glomerulonephritis. The study is summarized in tables 2 and 3. The results obtained in the normal subjects, in those with one kidney and in the patients with hypertension and nephritis were qualitatively similar, and are therefore considered together. It will be seen from a consideration of the data that renal function may be either unchanged or depressed by the action of the nitrite. In no case was there any improvement in renal function. In eleven of the subjects in whom both urea and creatinine clearance tests were performed, and in three in whom urea tests alone were done, there was no evidence of any significant changes in renal activity. In thirteen cases the nitrite caused a reduction in both urea and creatinine clearance. In eight cases there was also a distinct reduction in the total urinary output during the test period, which in six cases reached striking proportions. In eight instances either the creatinine was reduced and the urea was maintained essentially unchanged or the reverse was found. Of the four cases in which this discrepancy was striking, three showed a reduction in the creatinine clearance while the urea clearance was unchanged. The fifth showed the reverse. The interpretation of the findings in these eight cases is difficult. It is conceivable that the nitrite acted on the kidneys so that the usual proportion of back diffusion of urea did not take place in the tubules, and a relatively greater or less amount of urea was excreted than is usual, compared with the total glomerular filtration. It is more probable, however, that the discrepant results were due largely to a summation of the errors inherent in the technical procedures. Once, in case 20, the volume of urine was apparently distinctly increased by the action of the nitrite, but in spite of this there was no evidence of increased glomerular filtration as measured by the urea and creatinine procedures. In twenty-one of the thirty-five cases the nitrite caused a significant lowering of the arterial blood pressure. There was, however, strikingly little correlation between the degree of lowering of the pressure and the decrease in renal function. In those cases in which the drop was extreme, usually accompanied by pronounced symptoms, the urinary output and the excretion of creatinine and urea were ordinarily greatly diminished, but this was by no means invariable. For example, in case 34, in which the nitrite caused the systolic blood pressure to fall 100 mm. and marked cyanosis and a stuporous condition to develop, the urea clearance was only moderately reduced, and the creatinine clearance volume of urine remained unaltered. On the other hand, in several subjects who showed no change in systemic blood pressure, renal function was decreased definitely by the drug.

The subjects investigated had either normal kidneys or all degrees of renal damage, and yet no correlation between the state of the renal

reserve and the effect of the nitrite was observed. Moreover, the patients with hypertension exhibited varying degrees of peripheral arteriosclerosis, and yet no qualitative difference in the action of the nitrite could be ascertained under these circumstances.

#### COMMENT

The vascular action of sodium nitrite is chiefly, if not entirely, on the peripheral vascular system, and it produces vasodilatation probably as the result of direct action on the smooth muscle of the vessel walls.<sup>12</sup> The site of its activity, therefore, must be chiefly on the arterial side of the vascular bed. There is little or no evidence that in man sodium nitrite produces any direct effect on the capillaries or venules. The fact that the cardiac output is not significantly altered by the drug indicates that if arteriolar relaxation is produced, it is proportionate to the fall of the systemic arterial pressure. The vasomotor center either is unaffected or may be somewhat stimulated as the result of the cerebral ischemia occasioned by the fall in blood pressure.<sup>13</sup>

The action of sodium nitrite differs radically from that of certain other vasodilator substances both pharmacologically and clinically. The symptoms of intense flushing, almost invariably present when histamine or acetylcholine is injected owing to the dilatation of the capillaries and venules of the skin,<sup>14</sup> was absent in all of the fifty-three cases. Moreover, the fact that these two drugs, even in large doses, seldom produce a marked drop in blood pressure suggests either that they cause little or no arteriolar relaxation or that the site of their activity is confined to localized regions of the body; in particular, the splanchnic area may be spared. In contrast to such drugs, sodium nitrite usually produces some, and frequently a very marked, reduction in the arterial blood pressure, which may be unaccompanied by any symptoms whatsoever. The most dramatic symptom which may occur is fainting, and this manifestation was never seen as the result of the administration of histamine or acetylcholine.

In an endeavor to discover whether the depressing effect of the drug on the blood pressure is due either to direct action on the heart or to a diminished cardiac output secondary to decreased venous return, estimations of the minute volume output of the heart were performed. It was found that this did not change materially even in the presence of a

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12. Sollmann, T.: *A Manual of Pharmacology*, ed. 3, Philadelphia, W. B. Saunders Company, 1926, p. 494.

13. Pilcher, J. D., and Sollmann, T.: *Studies on the Vasomotor Centre: I. The Effects of the Nitrite Group*, *J. Pharmacol. & Exper. Therap.* **6**:323, 1915.

14. (a) Weiss, Soma; Robb, G. P., and Ellis, L. B.: *The Systemic Effects of Histamine in Man, With Special Reference to the Responses of the Cardiovascular System*, *Arch. Int. Med.* **49**:360 (March) 1932. (b) Ellis and Weiss.<sup>7</sup>

considerable drop in the arterial pressure, although the output per beat was usually somewhat decreased. This state of affairs rules out the possibility that a reduction in the arterial blood pressure is due primarily to a depression of the cardiac minute output.

In a number of instances reduction in the systolic pressure occurred without change in the diastolic pressure or in the blood flow through the heart. A decrease in the systolic blood pressure without change in the output of the heart suggests widening of the lumens of the larger arteries. In view of these changes in the cardiovascular system, the depressor effect on the systolic blood pressure can be explained as due to the following factors, singly or combined: (*a*) a relaxation of the larger arteries and (*b*) a decrease in the stroke volume output of the heart. Thus, the increased volume of the arterial system, resulting from relaxation of the vessel wall, is able to accommodate with a decreased systolic pressure the normal or decreased stroke volume output of the heart. That such a widening of the larger arteries actually occurs is supported by the observation that sodium nitrite causes a relaxation of the temporal and radial arteries and a more bounding pulse, even when there is no change in the stroke volume output of the heart or in the diastolic pressure.

It is well known that in certain types of hypertension, particularly in the malignant form and in eclampsia, the palpable and visible arteries are in a state of constriction. The retinal, temporal, radial, brachial and femoral arteries are examples. We have obtained by means of the roentgen rays, arteriograms of the vessels of the lower extremities during the injection of a solution of potassium iodide into the femoral artery. Comparison with arteriograms taken in normal subjects indicates that the arteries of the leg in certain cases of hypertension are in a state of constriction. It is this difference in the state of the larger arteries that may explain why, after the administration of sodium nitrite, the fall in the systolic blood pressure may be greater in patients with hypertension than in normal subjects.

In contrast to the changes noted in the systolic pressure, a marked drop in the diastolic pressure was seldom observed. Changes in the diastolic pressure are generally indications of alterations in the degree of peripheral arteriolar resistance. This comparative stability of the diastolic pressure suggests that the dilator effect of sodium nitrite on the small arteries and arterioles is not constant or marked. The behavior of those patients who reacted with only a moderate fall in the diastolic pressure and no change in the total blood flow through the heart, but yet showed cyanosis and fainting, suggests that the arteriolar dilatation occurs in different vascular areas to different degrees, with the result that the regional distribution of blood may be very irregular

although the total blood flow remains unaltered. One may assume from the observations in these cases, supported by experimental observations on animals, that a relatively pronounced dilatation of the splanchnic arteriolar system occurs, while the blood flow through the brain is decreased because of a lack of corresponding arteriolar relaxation. This variation in the response of various portions of the arteriolar area is probably due partly to the inherent physiologic characteristics of these vascular areas. However, the variation in the degree and extent of the degenerative vascular changes associated with hypertension in the individual organs is probably the dominating factor which determines the type of response to sodium nitrite in each patient. That the variations in the depressor effect of sodium nitrite are dependent on the state of the vascular system, rather than on a variable action of the drug, is supported also by the parallelism that exists between the effect of sodium nitrite and the depressor effect of stimulation of the carotid sinus in man. As with sodium nitrite, stimulation of the carotid sinus produces slight or no lowering of the blood pressure in normal persons, whereas a pronounced decrease in blood pressure is occasioned in patients with arterial hypertension.<sup>15</sup>

A comparison of the changes which take place in the human vascular system after the administration of histamine,<sup>14a</sup> of acetylcholine<sup>7</sup> or of sodium nitrite demonstrates in an impressive fashion the remarkably adaptable regulatory capacity of the human cardiovascular system. It not only reveals the intimate regulatory connection between the arteries, arterioles, capillaries, venules and veins, but shows that each of these vessels may have an independent function. Each division of the vascular system is capable of changing its caliber independently or in combination with another portion. The relative degree of sensitivity of the same type of vessel in different organs and of different types of vessels in the same organ to various chemical substances makes possible a delicate and economic functioning of the circulation through local or systemic chemical regulation. We have demonstrated how vasodilator chemical substances differ from each other in action and effect. This delicate chemical regulation not only is of significance in the direct regulation of blood vessels, but also has a fundamental association with the indirect reflex control of the circulation.

The literature concerning the effect of nitrite preparations on the function of the kidney presents results that are somewhat in conflict. In 1886 Dana<sup>16</sup> obtained diuresis in five normal persons and six patients

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15. Weiss, Soma, and Baker, J. P.: *The Carotid Sinus Reflex in Health and Disease: Its Rôle in the Causation of Fainting and Convulsions*, Medicine, to be published.

16. Dana, C. L.: *M. Rec.* **29**:255, 1886.



with renal disease following the administration of nitroglycerine. Loeb<sup>17</sup> felt that this drug had a deleterious effect on renal activity, since he found that in three patients there was a fall in urinary output after its administration. Elliott<sup>18</sup> was of the opinion that "there is no certain correspondence between the amount of urine excreted and the height of the blood pressure. Nitrites as often give an increase as a decrease in the urine output. Studies by Lawrence<sup>19</sup> showed that twelve of sixteen patients with hypertension who received sodium nitrite had an increase in the urinary output and in the phenolsulphonphthalein, total solid and nitrogen excretion. All of these patients also reacted by a lowering of the blood pressure. The reverse results were found by Mason.<sup>20</sup> He performed the Volhard water test on twenty patients, most of whom had hypertension, both under normal conditions and when sodium nitrite was given in 1 grain doses every half hour. In sixteen there was a decrease in water excretion and in four an increase. There was no ascertainable relationship to changes in the systolic or pulse pressure. Cushny<sup>21</sup> stated that "the kidneys are not much affected; occasionally a slight increase in the urine is observed, at other times a decrease, and after large quantities anuria may occur."

The effect of sodium nitrite on the renal activity is entirely due to its vascular action. If the local vasodilatation in the kidneys maintained or increased the glomerular blood pressure and improved renal blood flow, one would expect renal function to increase. Actually in the cases studied by us this never occurred. In one case there appeared to be an increase in urinary output, but the other tests showed no improvement of function. When there is a distinct reduction of the systemic blood pressure it may react unfavorably on the renal blood flow and decrease the renal function. This was by no means an invariable occurrence, however, and in the cases in which the urinary output of solids and water was maintained in the face of a drop in the blood pressure, the local renal vasodilatation must have compensated for the reduction in systemic blood pressure so that the effective filtering pressure remained unaltered.

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17. Loeb, A.: *Klinische Untersuchungen über den Einfluss von Kreislaufsänderungen auf die Urinzusammensetzung*, *Deutsches Arch. f. klin. Med.* **84**:579, 1905.

18. Elliott, A. R.: *The Treatment of Arterial Hypertension*, *Am. J. M. Sc.* **140**:6, 1910.

19. Lawrence, C. H., Jr.: *The Relation of Hypertension to Urinary Excretion*, *Am. J. M. Sc.* **144**:330, 1912.

20. Mason, E. C.: *A Note on Water Excretion as Influenced by Blood Pressure Response to Sodium Nitrite*, *J. Lab. & Clin. Med.* **9**:529, 1924.

21. Cushny, A. R.: *A Textbook of Pharmacology and Therapeutics*, ed. 7, Philadelphia, Lea & Febiger, 1918, p. 392.

In certain cases the renal function was reduced, although the general arterial blood pressure remained essentially unaltered. In these subjects the local vascular changes occurring in the kidneys may have been of such a nature as to decrease the glomerular capillary pressure, and probably consisted in a relatively greater dilatation of the efferent than of the afferent glomerular vessels.

The alterations in renal activity, when they did occur, were largely in the nature of a reduction in glomerular filtration. Changes in tubular activity were less frequent and rarely striking.

Any vasodilating drug which fulfils the criteria demanded in the treatment of arterial hypertension should have a constant, sustained action, should act by dilating the arterioles over all the constricted areas, should not give rise to unpleasant symptoms or side effects and should maintain the normal function of the organs, particularly of the heart and kidneys.<sup>22</sup> These criteria are not fulfilled by the inconstant and transitory action of sodium nitrite. The drug at times produces severe unpleasant symptoms, which are frequently unrelated to the magnitude of the decrease in blood pressure, and may cause depression of renal activity. Although sodium nitrite may have some place in the treatment of vascular crises associated with arterial hypertension, it is of no value in the daily treatment of the condition, and its employment in patients in whom renal insufficiency already exists is irrational.

#### SUMMARY

1. The study concerns the effect of large therapeutic doses (from 1 to 5 grains) of sodium nitrite by mouth on ten normal persons, twenty-nine patients with primary arterial hypertension, five patients with glomerulonephritis and nine patients on whom unilateral nephrectomy had previously been performed. Qualitatively the effect was the same in each group, but there were certain quantitative differences between the normal subjects and those with hypertension and renal disease.

2. The nitrite inconstantly produced symptoms, an increase in cardiac rate and a depression of blood pressure and renal function. No simple correlation was found between these factors except when they were markedly altered.

3. A decrease of systolic blood pressure was the most frequently observed effect of sodium nitrite. This was caused probably by dilatation of certain parts of the arterial system. The greater the initial degree of arterial tonus, the greater was the drop in systolic pressure. With arterial hypertension this was particularly evident.

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22. Weiss, Soma, and Ellis, L. B.: *The Rational Treatment of Arterial Hypertension*, J. A. M. A. **95**:846 (Sept. 20) 1930.

4. In five normal persons sodium nitrite produced no change in the minute volume output of the heart. In five patients with arterial hypertension this output was doubtfully reduced in three, and reduced 15 and 32 per cent respectively in two. In nine of these ten subjects there was a reduction of the cardiac stroke volume output, which reached 15 per cent or more in six.

5. Sodium nitrite did not affect the basal metabolic rate of nine of ten subjects; it possibly increased the rate in one.

6. The effect of the nitrite on renal function was investigated thirty-five times by simultaneous determinations of the urinary output and urea and creatinine clearance tests. In no case was the renal activity improved. In fourteen instances there was no change in renal function; thirteen times it was definitely decreased, and on eight occasions it was questionably lowered.

7. Physiologic changes which occur in the human cardiovascular system as a result of the action of sodium nitrite are discussed and correlated.

8. The use of sodium nitrite in the routine treatment of arterial hypertension with the hope of maintaining the blood pressure at a relatively low level is illogical and may be dangerous.

Miss Rose Shore and Miss Mary D. Baker furnished technical aid in this investigation.

# A COMPARATIVE STUDY OF BLOOD CULTURES TAKEN WITH KENDALL AND ROUTINE MEDIUMS

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The failure or difficulty of cultivating artificially the etiologic agents in a number of so-called virus diseases which are contagious and probably infectious, such as smallpox, influenza, poliomyelitis and others, has often been ascribed to improper mediums. Recently Kendall<sup>1</sup> expressed the belief that the difficulty in cultivating viruses was due to a departure of the mediums commonly employed from the environment of the organisms in nature. He pointed out that the artificial mediums usually employed contain protein degradation products (peptones and meat extracts) and little or no unaltered protein, whereas the body tissue possesses the unaltered protein without its hydrolytic products. In order to provide an artificial environment more nearly simulating the natural one in this respect, he prepared a medium (K medium) containing the unaltered protein without peptones or other substances resulting from its disintegration.

With this medium Kendall claimed to have isolated from the blood of three patients with influenza a coccus which existed in the blood in a filtrable state, but which by repeated transplants in K medium and subcultures on agar could be transformed into a visible, nonfiltrable organism. In the filtrable form it grew on K medium, but did not grow visibly in peptone medium. Injection of the coccus in the filtrable state into the rabbit induced an infection simulating influenza, but inoculations with the nonfiltrable (coccus) form were unsuccessful. Furthermore, Kendall claimed to have converted a number of other organisms into filtrable forms and to have recovered them, following filtration, in their ordinary nonfiltrable state. Among these were *Bacillus typhosus*, *Bacillus paratyphosus* A, *Staphylococcus aureus*, Noguchi's *Leptospira icteroides*, Dochez's scarlet fever streptococcus and Rosenow's poliomyelitis streptococcus. He also stated that staphylococcus phage filtrates and Besredka's staphylococcus antiviral had yielded typical cultures of *Staph. aureus*. Furthermore, Kendall stated that he had obtained positive growth in blood cultures quite readily in a series of cases of

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From the Department of Laboratories of the Mount Sinai Hospital.

1. Kendall, A. I.: Science **74**:129 (Aug. 7) 1931.

common cold, arthritis, rheumatic fever, rheumatoid endocarditis, measles (thirty hours before the rash) and German measles, while cultures on ordinary artificial mediums in the same cases gave no growth.

In the work to be reported I have made a comparative study of the results of blood cultures made according to Kendall's method employing the K medium and of results of simultaneous blood cultures made according to the routine method with the ordinary artificial mediums employed in the laboratories of the Mount Sinai Hospital.

#### METHOD

The routine method was performed as follows: The equipment, consisting of a sterile syringe and needle, three Petri dishes and mediums, was arranged on a sterile towel at the bedside. Fluid and solid mediums were used. There were three flasks of the former, each of 100 cc. capacity, containing about 75 cc., respectively, of plain broth, dextrose broth (2 per cent dextrose) and tomato-dextrose-peptone broth. Solid mediums were prepared by pouring three plates from tubes containing 10 cc. of plain agar, dextrose agar and liver hormone agar, respectively, with similar amounts of plain broth in tubes. While the equipment was being arranged, the tubes of agar were liquefied by being heated in boiling water. These were then cooled to from 45 to 50 F. in ice water provided at the bedside. From an arm vein, 21 cc. of blood was taken aseptically, and 2 cc. was added to each of the tubes of liquefied agar, dextrose agar and liver hormone agar. These were poured back and forth into the tubes of broth and then into the Petri dishes, where the mediums were permitted to harden. Five cubic centimeters of blood was inoculated into each of the three flasks. The flasks and plates were then incubated at 37 C. Subcultures from the flasks were made on the following day and repeated daily thereafter for several days (if no growth occurred) into 1 per cent dextrose broth and ascitic fluid plus 1 per cent dextrose agar slants. Plates and flasks were examined daily for four days.

During the course of this work the routine method was modified by substituting in place of the flask of tomato broth a 100 cc. flask containing 75 cc. of K medium prepared according to the method described by Kendall.<sup>1</sup> Fresh hog's intestine was opened, cleaned, ground in a meat chopper and immersed in four times its volume of a 95 per cent solution of alcohol. Extraction was carried out at 37 C. for two days with occasional stirring. The alcohol was then removed and extraction repeated with fresh alcohol (altogether three extractions). The dry tissue was then subjected to reextraction with benzene to remove the remaining lipoidal constituents. The benzene was removed by filtration, air current and exposure to the air for several days. The material that remained after extraction of the lipoidal elements was then reground to a fine powder. The powder when ready for use was added to Tyrode's solution (2 per cent by weight of dry intestine was used). The suspension was autoclaved and adjusted to a  $p_H$  of from 7 to 7.4 by means of sodium bicarbonate. Seventy-five cubic centimeters of the medium was used for each blood culture; it was placed in an Erlenmeyer flask of 100 cc. capacity, and this replaced the flask containing tomato medium in the routine method. For routine purposes, any given blood culture was performed as already described, using however only the two remaining routine flasks and the three routine plates. Somewhat more than the usual 21 cc. of blood was drawn, after 16 cc. of it (2 cc. in each of the three solid mediums

and 5 cc. in each of the two flasks) was inoculated into the routine mediums; the remaining 5 to 10 cc. was inoculated into the Kendall flask at the bedside. The routine flasks and plates were studied and subcultured as already described. The Kendall flask was simultaneously incubated at 37 C. Smears from the Kendall flask were made daily; if a smear was positive, or if clouding occurred, subcultures were made from this flask into one tube containing 10 cc. of K medium, one tube of 1 per cent dextrose broth and one tube of ascitic fluid plus 1 per cent dextrose agar. If the primary culture on K medium was negative, incubation was continued for ten days; then a transplant was made to another tube of K medium. After three such transplants at intervals of ten days, the medium of the final transplant was filtered through a Berkefeld N candle and streaked onto plates of peptone agar containing about 25 per cent K medium.<sup>2</sup> These plates were incubated at 37 C. anaerobically for three days and aerobically for four days and then examined for growth.

#### CLINICAL MATERIAL

Special cases were not chosen for this study; blood cultures were performed as a routine when they were requested by the medical, surgical and special divisions of the hospital. While the indications for these blood cultures differed somewhat in the various hospital services, the cultures were generally requested for patients of the following descriptions:

- Patients with the clinical features of a general infection (bacteremia), particularly when some local infection served as an obvious portal of entry
- Patients with an obvious local infection who, after operation, presented symptoms of a general infection
- Patients with the clinical features of typhoid fever or subacute bacterial endocarditis
- Patients with rheumatic cardiovalvular diseases with fever.
- Patients with otitic symptoms including fever, especially when thrombosis of a sinus or of the bulb of the jugular vein was suspected.
- Patients with fever of uncertain etiology
- Patients with lobar pneumonia and meningococcic meningitis
- Patients with terminal cystitis and ascending pyelonephritis

One hundred and three blood cultures were taken from seventy-seven patients. The clinical diagnoses on these patients may be classified as in table 1.

Most numerous were those cases (15, with twenty-three blood cultures) in which the presence of a local infection which might serve as an obvious portal of entry, combined with a protracted febrile course, suggested the possibility of a bacterial invasion of the blood stream. Under "local infection" are included cases of gonorrheal arthritis and salpingitis, suppurative adenitis, osteomyelitis and other suppurative

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2. Tubes of plain agar were melted in boiling water, mixed with 25 per cent by volume of K medium, poured into a Petri dish and permitted to harden. Except when otherwise indicated, all agar mediums contained peptone.

processes. The cases designated under "postoperative fever" were likewise associated with an infected focus and with continued fever, developing after operation or other surgical trauma, which suggested that a bacteremia had been precipitated. Another large group was formed by cases of acute otitis media or mastoiditis in which blood cultures were made to determine the presence of sinus thrombosis. In cases which presented a picture highly suggestive of, or definitely that of, subacute bacterial endocarditis, blood cultures were taken as a routine to confirm the diagnosis. There were, in addition, six cases of chronic cardiovalvular disease with fever, three of which presented the clinical features of acute articular rheumatism. Blood cultures were made in these cases because of the possibility of bacterial endocarditis without

TABLE 1.—*Summary of Clinical Material*

Diagnosis	Number of Cultures	Number of Patients
Local infection, including gonorrhea, arthritis and salpingitis..	23	15
Postoperative fever .....	10	8
Otitic infection .....	13	11
Subacute bacterial endocarditis.....	9	6
Chronic cardiovalvular disease with fever, including rheumatic fever .....	8	6
Genito-urinary infection .....	8	6
Pulmonary infection:		
Lobar pneumonia .....	9	7
Bronchopneumonia and upper respiratory infection....	4	4
Tuberculosis .....	2	2
Contagious diseases .....	7	5
Meningitis:		
Meningococcus .....	4	4
Pneumococcus .....	2	1
Metastatic carcinoma .....	4	2

the complete clinical manifestations. Eight blood cultures were made in six cases of genito-urinary infections in which, particularly in the terminal stages, bacterial invasion of the blood stream was apt to occur. Nine blood cultures were made in seven cases of lobar pneumonia. There were four cases of meningococcic meningitis in which blood cultures were taken early in the course of the disease. The remaining blood cultures were made in cases of bronchial pneumonia and infections of the upper respiratory tract, tuberculosis, contagious diseases, and metastatic carcinoma, generally on admission, when the differentiation from a general infection of the blood was not clear.

#### BACTERIOLOGIC RESULTS

Table 2 shows the comparative results obtained with the K medium and with routine culture mediums, the tomato flask being omitted.

In nineteen cultures, both methods gave positive growth, and both gave identical organisms. It is well to point out that in these instances

TABLE 2.—*Comparative Results of Blood Cultures Made with K Medium and by the Routine Technic*

Blood Culture		Diagnosis	Growth Obtained by	
			Routine Method	Kendall's Method
95	2	Pneumococcic meningitis	Staph. albus	Staph. albus
98	4	Lobar pneumonia	Pneumococcus, type III, in plain broth and on all plates	Pneumococcus, type III
110	7	Osteomyelitis of fourth lumbar vertebra	Staph. aureus in dextrose flask; no growth in other flasks or on plates	No growth
115	12	Subacute bacterial endocarditis	Str. viridans (a)	Str. viridans (a)
122	15	Lobar pneumonia	Pneumococcus, type I, in all except plain agar	Pneumococcus, type I
130	19	Lobar pneumonia	Pneumococcus, type IV, in all except plain agar	Pneumococcus, type IV
139	27	Meningococcic meningitis	Meningococcus	Meningococcus
141	28	Acute sinusitis; encephalomyelitis	Str. haemolyticus ( $\beta$ ) in flasks; no growth on plates	Str. haemolyticus ( $\beta$ )
142	29	Carcinoma of prostate with metastasis to bones	B. coli	B. coli
143	30	Furuncle of neck	Staph. albus	Staph. albus
150	35	Subacute bacterial endocarditis	Str. viridans (a)	Str. viridans (a)
165	47	Meningococcic meningitis	Meningococcus	Meningococcus
168	49	Suppurative inguinal adenitis	Staph. albus	No growth
172	51	Lobar pneumonia	Pneumococcus, type II, dextrose broth; no growth in plain broth	Pneumococcus, type II
174	53	Thrombosed prolapsed hemorrhoids, post-operative	Gram + cocci only anaerobically	No growth
188	64	Carcinoma of prostate with metastasis to bones	B. coli (no growth in plain flask)	B. coli
192	68	Epididymo-orchitis; post-operative peritonitis	Str. haemolyticus ( $\beta$ )	Str. haemolyticus ( $\beta$ )
199	71	Subacute bacterial endocarditis	Str. viridans (a)	Str. viridans (a)
215	82	Arsphenamine dermatitis	Staph. aureus in two flasks; no growth on plates	Staph. aureus
223	89	Subacute bacterial endocarditis	Enterococcus	Enterococcus
225	91	Carcinoma of prostate with metastasis to bones	B. coli	B. coli
233	98	Abscess of brain ?	Str. haemolyticus ( $\beta$ )	Str. haemolyticus ( $\beta$ )
240	103	Subacute bacterial endocarditis	Enterococcus	Enterococcus
94	1	Pyelonephrosis	No growth	No growth
97	3	Bilateral acute mastoiditis	No growth	No growth
104	5	Postoperative broncho-pneumonia	No growth	No growth
108	6	Meningococcic meningitis	No growth	No growth
111	8	Lobar pneumonia; phlebitis	No growth	No growth
112	9	Pneumococcic meningitis	No growth	No growth
113	10	Chronic cardiovalvular disease; bronchopneumonia	No growth	No growth
114	11	Lobar pneumonia	No growth	No growth
116	13	Meningococcic meningitis	No growth	No growth
121	14	Malaria	No growth	No growth
123	16	Perinephritic abscess	No growth	No growth
128	17	Suppurative adenitis	No growth	No growth
129	18	Cholelithiasis and cholecystitis (postoperative)	No growth	No growth
131	20	Osteomyelitis of fourth lumbar vertebra	No growth	Gram-positive cocci which did not grow out
132	21	Hydrosalpinx; post-operative pneumonia	No growth	No growth
133	22	Chronic cardiovalvular disease	No growth	No growth
134	23	Lobar pneumonia	No growth	No growth
136	24	Acute mastoiditis	No growth	No growth



TABLE 2.—*Comparative Results of Blood Cultures Made with K Medium and by the Routine Technic—Continued*

Blood Culture	Diagnosis	Growth Obtained by	
		Routine Method	Kendall's Method
137 25	Subacute bacterial endocarditis	No growth	No growth
138 26	Inguinal hernia, post-operative	No growth	No growth
145 31	Mastoiditis	No growth	No growth
146 32	Acute otitis media	No growth	No growth
147 33	Acute otitis media	No growth	No growth
149 34	Lobar pneumonia	No growth	No growth
152 36	Suppuration of the neck	No growth	No growth
153 37	Upper respiratory infection; posttonsillectomy fever	No growth	No growth
154 38	Amputation of leg	No growth	No growth
155 39	Rheumatic fever	No growth	No growth
156 40	Mastoiditis	No growth	No growth
157 41	Lobar pneumonia	No growth	No growth
158 42	Incomplete abortion	No growth	No growth
159 43	Furuncle of neck	No growth	No growth
161 44	Abscess of finger; lymphangitis	No growth	No growth
163 45	Acute otitis media	No growth	No growth
164 46	Rheumatic fever	No growth	No growth
167 48	Subacute bacterial endocarditis	No growth	No growth
171 50	Infected thrombosed hemorrhoids; post-operative fever	No growth	No growth
173 52	Osteomyelitis of fourth lumbar vertebra	No growth	No growth
175 54	Rheumatic fever	No growth	No growth
177 55	Typhus	No growth	No growth
178 56	Epididymo-orchitis; post-operative peritonitis	No growth	No growth
179 57	Gangrenous ulceration of skin of neck	No growth	No growth
180 58	Gonorrheal salpingitis	No growth	No growth
182 59	Upper respiratory infection; broncho-pneumonia	No growth	No growth
183 60	Subacute bacterial endocarditis	No growth	No growth
184 61	Acute mastoiditis; erysipelas	No growth	No growth
186 62	Acute mastoiditis; erysipelas	No growth	No growth
187 63	Acute otitis media	No growth	No growth
189 65	Typhus fever	No growth	No growth
190 66	Disseminated broncho-pneumonia	No growth	No growth
191 67	Acute mastoiditis	No growth	No growth
194 69	Typhus fever	No growth	No growth
195 70	Chronic cardiovalvular disease	No growth	No growth
200 72	Primary thrombosis of bulb of jugular vein	No growth	No growth
201 73	Rheumatic fever; chronic cardiovalvular disease	No growth	No growth
202 74	Chronic glomerulonephritis, exacerbated	No growth	No growth
203 75	Bronchopneumonia	No growth	No growth
204 76	Ascending pyelonephritis	No growth	No growth
206 77	Bronchopneumonia	No growth	No growth
208 78	Cystectomy for carcinoma of bladder; postoperative fever	No growth	No growth
210 79	Abscess of brain	No growth	No growth
211 80	Carcinoma of cecum with metastasis	No growth	No growth
214 81	Empyema; phlegmon of thoracic wall	No growth	No growth
217 83	Bronchopneumonia	No growth	No growth
218 84	Ulcerative colitis	No growth	No growth
219 85	Diabetes; otitis media	No growth	No growth
220 86	Ascending pyelonephritis	No growth	No growth
221 87	Erysipelas; carcinoma of pancreas	No growth	No growth
222 88	Infectious mononucleosis	No growth	No growth

TABLE 2.—*Comparative Results of Blood Cultures Made with K Medium and by the Routine Technic—Continued*

Blood Culture	Diagnosis	Growth Obtained by	
		Routine Method	Kendall's Method
224 89	Scarlet fever	No growth	No growth
226 92	Brill's disease	No growth	No growth
227 93	Ascending pyelonephritis	No growth	No growth
229 94	Rheumatic fever	No growth	No growth
230 95	Disseminated miliary tuberculosis	No growth	No growth
231 96	Subacute bacterial endocarditis	No growth	No growth
232 97	Ascending pyelonephritis	No growth	No growth
234 99	Acute glomerulonephritis	No growth	No growth
235 100	Suppuration of neck	No growth	No growth
236 101	Chronic glomerulonephritis	No growth	No growth
237 102	Lobar pneumonia	No growth	No growth

the results with the routine method were based on the findings in two flasks and three plates containing 16 cc. of blood. Thus in any given positive result one or more of these five units may have shown no growth. On the other hand, the positive growths obtained with the K medium were found in single flasks each of which had been inoculated with from 5 to 10 cc. of blood. Thus, in culture 4, the routine medium as well as the K medium showed *Pneumococcus*, type III, but the plain broth flask was negative. Similarly in blood culture 51 *Pneumococcus*, type II, did not grow in the plain broth flask. Similar instances in which positive growths by the routine method were obtained in less than the entire five units follow: In culture 64, the plain flask was negative for *Bacillus coli*; in cultures 15 and 19, *Pneumococcus* did not grow on the plain agar plates; in culture 82, *Staph. aureus* did not grow on any of the plates.

On the other hand, there were four cultures in which positive results were obtained by the routine method and negative results by use of the K medium. In culture 7, representing a case that clinically appeared to be one of osteomyelitis of the fourth lumbar vertebra running a septic course, *Staph. aureus* grew out in the dextrose flask, but not in the other flask or on the plates. The Kendall flask was likewise negative. It is well to note that in a later culture made from the same patient's blood (culture 20) the result was negative by both the routine and the Kendall method. In culture 30, representing a case of furunculosis of the neck, the routine method produced one colony of *Staph. albus* per cubic centimeter; the Kendall flask was negative. In culture 53, the routine aerobic mediums as well as the Kendall medium, showed no growth, but the anaerobic medium yielded gram-plus cocci. This culture was from a patient who had been operated on for thrombosed, infected hemorrhoids. An earlier aerobic culture of this patient's blood (culture 50) was negative on both the routine mediums and the Kendall

medium. Finally, routine culture of the blood of a patient with suppurative inguinal adenitis and a septic temperature curve showed two colonies of *Staph. albus* per cubic centimeter, while culture of the blood on the K medium showed no growth. I observed, therefore, that cultures on the K medium showed no growth in those instances in which the cultures by the routine method indicated an invasion of the blood stream with few organisms, or in which by the routine method only individual plates or flasks showed positive growth, or in which growth was obtained only by anaerobic culture. The remaining seventy cultures both on the routine mediums and on the K medium gave negative results. Further study was conducted to determine whether or not in a number of cases filtrable forms of an organism were present which might be transformed to the ordinary nonfiltrable state, and also to determine whether or not it was possible to convert the common organisms obtained in the positive cultures into filtrable forms and then recover them in a nonfiltrable state as claimed by Kendall.

When a culture on K medium was positive, it was subcultured in a tube containing 10 cc. of K medium. This was incubated ten days. Subculture was then repeated at intervals of ten days until three subcultures had been obtained. Smears were made at this point from the final subculture; if a smear was positive, the organism was isolated. The final subculture was then filtered rapidly through a small Berkefeld N filter. The filtrate was streaked onto plates containing agar with about 25 per cent of K medium. Smears were made of the filtrate; if a smear was positive, the organism was isolated. The plates were then incubated for three days at 37 C. in anaerobic jars<sup>3</sup> and then aerobically for four days.

When a culture on K medium was negative, the original flask was incubated ten days before subcultures were made, and the identical procedure used with the positive culture was followed. Table 3 shows the results obtained.

Of nineteen positive cultures, eleven were preserved through three subcultures. Before filtration the organisms were clearly visible on smear and could be isolated on ordinary mediums or on K medium. After the third subculture from each positive growth had been passed through a Berkefeld N candle, the organisms were present in four of the filtrates and on incubation anaerobically and aerobically grew out on the hog's intestine-agar plates.<sup>4</sup>

Two of these were enterococci,<sup>5</sup> one was *Bacillus coli*, and one was *Staph. aureus*. The other seven cultures in repeated subcultures of

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3. Cohen, J.: *J. Lab. & Clin. Med.* **15**:262 (Dec.) 1929.

4. These plates contained plain agar with 25 per cent of Kendall's hog's intestine medium, as described under "Methods."

5. These were gram-positive, nonhemolytic cocci, growing in chains and "diplo" forms, which fermented esculin.

which the organisms remained visible, gave no visible organisms on filtration, nor any growth on transfer to and incubation of the agar plates. Similarly the eight positive cultures in which the organisms could not be preserved on subcultures, gave no growth after filtration or on transfer to the agar plates. Thus the ordinary organisms, when

TABLE 3.—*Summary of Results with Cultures on K Medium*

Blood Culture	Original K Culture	Before Filtration After 3 Subcultures	After Filtra- tion	After 7 Days' Incubation
95 2	Staph. albus	No growth	No growth	No growth
98 4	Pneumococcus, type III	No growth	No growth	No growth
115 12	Str. viridans	No growth	No growth	No growth
122 15	Pneumococcus, type I	Pneumococcus, type I	No growth	No growth
130 19	Pneumococcus, type IV	No growth	No growth	No growth
139 17	Meningococcus	No growth	No growth	No growth
141 28	Str. haemolyticus ( $\beta$ )	No growth	No growth	No growth
142 29	B. coli	B. coli	No growth	No growth
143 30	Staph. albus	No growth	No growth	No growth
150 35	Str. viridans	Str. viridans	No growth	No growth
165 47	Meningococcus	No growth	No growth	No growth
172 51	Pneumococcus, type II	No growth	No growth	No growth
188 64	B. coli	B. coli	B. coli	B. coli
192 68	Str. haemolyticus ( $\beta$ )	Str. haemolyticus ( $\beta$ )	No growth	No growth
199 71	Str. viridans	Str. viridans	No growth	No growth
215 82	Staph. aureus	Staph. aureus	Staph. aureus	Staph. aureus
223 89	Enterococci	Enterococci	Enterococci	Enterococci
225 91	B. coli	B. coli	No growth	No growth
233 98	Str. haemolyticus ( $\beta$ )	Str. haemolyticus ( $\beta$ )	No growth	No growth
240 103	Enterococcus	Enterococcus	Enterococcus	Enterococcus
94 1	No growth	No growth	No growth	No growth
97 3	No growth	Diphtheroids (contaminant)	No growth	No growth
104 5	No growth	No growth	No growth	No growth
108 6	No growth	No growth	No growth	No growth
110 7	No growth	No growth	No growth	No growth
111 8	No growth	No growth	No growth	No growth
112 9	No growth	No growth	No growth	No growth
113 10	No growth	No growth	No growth	No growth
114 11	No growth	B. subtilis (contaminant)	No growth	No growth
116 13	No growth	B. subtilis (contaminant)	No growth	No growth
121 14	No growth	No growth	No growth	No growth
123 16	No growth	No growth	No growth	No growth
128 17	No growth	Diphtheroids	Diphtheroids	Diphtheroids
129 18	No growth	No growth	No growth	No growth
131 20	No growth	No growth	No growth	No growth
132 21	No growth	No growth	No growth	No growth
133 22	No growth	No growth	No growth	No growth
134 23	No growth	No growth	No growth	No growth
136 24	No growth	B. subtilis	B. subtilis	B. subtilis
137 25	No growth	Diphtheroids	Diphtheroids	Diphtheroids
138 26	No growth	No growth	No growth	No growth
145 31	No growth	No growth	No growth	No growth
146 32	No growth	No growth	No growth	No growth
147 33	No growth	No growth	No growth	No growth
149 34	No growth	No growth	No growth	No growth
152 36	No growth	No growth	No growth	No growth
153 37	No growth	No growth	No growth	No growth
38-45	No growth	No growth	No growth	No growth
164 46	No growth	Diphtheroids (contaminant)	No growth	No growth
48-50	No growth	No growth	No growth	No growth

obtained from blood cultures, could not be converted into filtrable forms, and transfer to ordinary mediums did not restore the usual nonfiltrable state.

Of the eighty-three cultures that in the original Kendall flasks were negative, nine were contaminated after being subcultured three times, six by diphtheroids and three by *Bacillus subtilis*. In four cultures, the contaminants passed through the Berkefeld filters (in three, diphtheroids; in one, *B. subtilis*) and were grown in pure culture on

the hog's intestine-agar plates after seven days' incubation, as previously described. The seventy-four cultures that remained persistently negative on subculture in the Kendall tubes gave no growth in any case on being transplanted to ordinary peptone medium. That is, in no instance in which a routine blood culture failed to show growth was a positive result obtained in the original Kendall flask or on repeated subculture, filtration and incubation on ordinary mediums, so that there was no possibility of invisible, filtrable forms of organisms being present in the blood of any of these patients.

#### COMMENT

In this study I have considered the K medium from two points of view; first, that of its employment in routine blood cultures and, second, that of its alleged capacity for isolating filtrable forms of various organisms. In regard to the first, I have observed the results obtained by the use of K medium in comparison with those obtained by the routine procedure practiced in the laboratories of the Mount Sinai Hospital. In one hundred and three cultures there were four discordant results; i. e., the K medium failed to isolate organisms obtained by the ordinary procedure. Any comparison of results obtained by the routine mediums with those obtained by the K medium must include a consideration of the quantity of blood and of the quantity and quality of the mediums employed.

Ordinarily, 21 cc. of blood is used in the routine method for blood cultures. After the flask of K medium was substituted for the tomato flask, only 16 cc. of blood was taken for the routine mediums and only from 5 to 10 cc. (generally about 8 cc.), or half as much, was inoculated into the flask of K medium. Likewise considerably less medium was employed in the K flask than in the ordinary procedure. Still the increased accuracy represented in the four additional positive cultures when only nineteen of one hundred cultures were positive appears to be of sufficient significance to justify the importance of the larger quantities of blood and medium used in the laboratories of this hospital. It is possible, however, to compare the results obtained with the flask of K medium with those obtained in any one of the other flasks, as these were inoculated with only 5 cc. of blood. In that case one finds that whereas the flasks of K medium failed to grow organisms in four instances in which the routine mediums combined gave growth, the dextrose broth flask failed to grow organisms in only one instance, and the plain broth flask, in five instances. There were, furthermore, five instances in which one or more of the plates containing solid medium failed to grow organisms when a positive culture was obtained. Thus, considered as a single unit, the flask of K medium was inferior to the dextrose flask and somewhat superior to the plain broth flask.

There are, in addition, other advantages of the routine method, some of which were not brought out in this study. Thus it was found by Lichtman and Gross<sup>6</sup> that in a small percentage of cases which clinically appeared to be of rheumatic fever, nonspecific ulcerative colitis,<sup>7</sup> chronic cardiovalvular disease, rheumatoid arthritis, aplastic anemia, pernicious anemia, meningococcic meningitis, pyelitis, pyelonephritis, leukemia and nephritis, a nonhemolytic streptococcus was grown from the blood stream in fluid but not in solid medium owing to an insufficient number of organisms, as smaller amounts of blood are inoculated into the solid medium, and the mortality on solid medium is greater. Hence, unless the organisms in the blood stream are sufficiently numerous, no growth will be obtained on solid medium. This feature, as pointed out earlier by Libman,<sup>8</sup> has generally aided in distinguishing a transitory invasion of the blood stream by streptococcus from the bacteremia of subacute bacterial endocarditis, in which the organisms are generally sufficient to give growth in both fluid and solid mediums. Furthermore, the use of the K medium alone without solid mediums as employed in the routine method would provide great difficulty in isolation of the causative organisms when a mixed infection is present. Another objection is the longer period required with the use of only a Kendall flask before a given organism is isolated from the blood stream. With the routine method, it is often possible to determine the organism from the primary culture, i. e., without further subculture. This is particularly true when the organism is a streptococcus which appears on the blood plate. With the K medium, further subculture onto solid medium is necessary before identification. Finally, the greater cost and difficulty and the much longer time required for preparation of the medium seriously militate against its use in place of the mediums ordinarily employed.

Claims for the existence of filtrable forms of ordinary organisms as proposed by Kendall have been made also by a number of other investigators. Recently Hauduroy<sup>9</sup> summarized the evidence for invisible, filtrable forms of visible bacteria and discussed a number of such organisms. Since the experiments of Fontes<sup>10</sup> and of Vaudremer<sup>11</sup>

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6. Lichtman, S. S., and Gross, Louis: Streptococci in Blood in Rheumatic Fever, Rheumatoid Arthritis and Other Diseases Based on a Study of 51,233 Consecutive Blood Cultures, *Arch. Int. Med.* **49**:1078 (June) 1932.

7. Crohn, B. B., and Schwartzman, G.: *J. Lab. & Clin. Med.* **14**:722 (May) 1929.

8. Libman, E.: Characterization of Various Forms of Endocarditis, *J. A. M. A.* **80**:813 (March 24) 1923.

9. Hauduroy, P.: *J. de physiol. et de path. gén.* **25**:254, 283, 522 and 537 1923.

10. Fontes, A.: *Mem. Inst. Oswaldo Cruz* **1**:51, 1909.

11. Vaudremer, A.: *Compt. rend. Soc. de biol.* **89**:80 (June 9) 1923.

the presence of such filtrable, invisible forms of the tubercle bacillus has been maintained. More recently Kahn and Torrey<sup>12</sup> described various forms of this organism forming a complete cycle.

In the blood cultures considered in this study, I sought first to determine the possibility of such filtrable, invisible forms being present in the blood of febrile patients in whose blood the routine cultures showed no growth, and second to determine whether ordinary organisms by repeated subculture in tubes of K medium could be converted into these invisible forms which would pass through a filter and reappear when cultivated on ordinary solid medium. In no instance did I succeed in obtaining such forms regardless of whether the original culture on K medium showed growth or not. This coincides with the findings recently reported by Craig and Johns,<sup>13</sup> who noted that *B. typhosus*, *Corynebacterium diphtheriae*, *Staph. albus* and *Str. viridans* grew poorly or were lost on subculture when grown on K medium, and when filtered and transferred to ordinary mediums, gave no growth. Of the nineteen positive cultures in the K flask, eight were lost on subculture. None of these reappeared after filtration and transfer to solid medium.

More interesting perhaps were the eleven cultures that remained viable through the three subcultures and up to the point of filtration. Four of these passed through the Berkefeld N filters not as invisible forms, but in their ordinary guise, clearly detectable on smear and on further culture. This becomes more significant with the detailed study of filtrability made by Varney and Bronfenbrenner<sup>14</sup> with various cultures in K medium. They showed that there was a greater incidence of passage of viable units from K cultures than from cultures on ordinary mediums, and that there are substances in the K medium which break down the efficiency of these filters, rendering them more permeable to bacterial suspensions made either in K medium, saline solution or broth when these suspensions are filtered just after passage of sterile K medium.

#### SUMMARY

1. One hundred and three routine blood cultures were made for seventy-seven patients suffering from a variety of febrile illnesses suggesting the presence of bacteremia. Simultaneously, flasks containing K medium were inoculated with blood from these patients.

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12. Kahn, M. C., and Torrey, J. C.: *Tr. Nat. A. Prev. Tuberc.* **24**:264, 1928; *Am. Rev. Tuberc.* **18**:815 (Dec.) 1928.

13. Craig, C. F., and Johns, F. M.: *Proc. Soc. Exper. Biol. & Med.* **29**:661 (Feb.) 1932.

14. Varney, P. L., and Bronfenbrenner, J.: *Proc. Soc. Exper. Biol. & Med.* **29**:804 (April) 1932.

2. The K medium showed 4 per cent less positive results than the ordinary routine method. Compared with the individual flasks and plates used in the ordinary method, the flask of K medium showed slight inferiority to some and slight superiority to other individual units.

3. Other disadvantages were found in the difficulty and expense of preparing the medium and the greater time necessary before an organism could be identified.

4. Repeated subcultures from the original K flask failed to show any invisible, filtrable forms which could be converted to the ordinary state by transfer to solid medium as alleged by Kendall. There was no evidence in the cases studied to show that the clinical picture was due to a filtrable, invisible form of an organism which did not show itself on the ordinary mediums.

5. In several instances common organisms were found to pass through the Berkefeld filter, suggesting the possibility that the K medium may have had some influence in impairing the efficiency of the filter.



# AN UNUSUAL BLOOD GROUP

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It was observed, in the course of blood grouping and matching, that certain bloods apparently belonging to group II did not match. In an attempt to find why these bloods did not match the serums were tested with known cell suspensions and some were found to be group IV (Moss). It was then discovered that the serum used as known group III agglutinated some group IV cells, and a thorough study of this serum was undertaken.

The agglutination reactions of this serum ( $\text{III}_1$ ) were tested with eight group I, seventy-two group II, fifteen group III and a hundred group IV cell suspensions. The cells from our subject were tested with seven group III, three group I and several group II serums. The results are given in table 1. The method used in all agglutination tests was as follows: Two drops of serum were mixed on a clean slide with one drop of a cell suspension in a solution of 1 per cent sodium citrate in 0.85 per cent sodium chloride. The slides were kept at room temperature in covered petri dishes containing moistened filter paper to prevent drying. The slides were rotated to insure mixing and were examined at intervals. A result was not reported as negative until after examination at thirty minutes or more.

Note in table 1 that this group  $\text{III}_1$  serum differs from typical group III serum in that it agglutinated 33 per cent of the fifteen group III cells examined and 47 per cent of the hundred group IV cells examined. The cells differ from typical group III cells in that they were agglutinated by 43 per cent of the seven group III serums tested. The presence of agglutination could be detected macroscopically. The extent of the agglutination would be graded 2 to 3 plus if the agglutination of group II cells is regarded as 4 plus. The appearance of the clumps is identical with that of the clumps of group II cells.

To prove further that this was an iso-agglutinin and not a pseudo-agglutinin, absorption experiments were done. The results of these experiments are summarized in table 2. The cells used for absorption

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were all agglutinated by this serum. It is evident that there are at least two types of group II cells. That corresponding to II<sub>B</sub> in table 2 contains an agglutinin reacting with the unusual agglutinin in this group III<sub>1</sub> serum as well as the usual agglutinin reacting with group III serum. The other group II cells contain only the typical agglutinin. The results shown in the table may be explained by the presence of a single extra agglutinin in this group III<sub>1</sub> serum and of a corresponding single agglutinin occurring in some of the cells in each of

TABLE 1.—*Agglutination Reactions of Group III<sub>1</sub> Serum \**

Classifications			Serum				
Landsteiner	Jansky	Moss Cells	I	II	III	III <sub>1</sub>	IV
AB	IV	I	0	+	+	+	+
A	II	II	0	0	+	+	+
B	III	III	0	+	0	+	+
		III <sub>1</sub>	0	+	+	0	+
					(43% of serums)		
0	I	IV	0	0	0	+	0
						(47% of cells)	

\* + = agglutination; 0 = no agglutination.

TABLE 2.—*Results of Absorption Experiments.*

Cells	Serum III <sub>1</sub> Absorbed with Cells			
	II <sub>B</sub>	II <sub>W</sub>	III <sub>K</sub>	IV <sub>M</sub>
II <sub>B</sub>	0	+	+	+
II <sub>W</sub>	0	0	+	+
III <sub>K</sub>	0	+	0	0
IV <sub>M</sub>	0	+	0	0

the three groups tested. It is probable that this agglutinin could also be found in group I cells.

The serums were kept in the icebox, but no special precautions were taken to keep them sterile. Fresh serum of group III<sub>1</sub> was taken from time to time and duplicate experiments done. The agglutinating properties remained constant for several months.

When the agglutination reactions were carried out at 37 C., the agglutination with group IV cells was somewhat less marked, but still very definite.

Investigation of the family showed that the father belonged to group IV, the mother to group I, a sister to group II and a brother to group III. Neither the mother's nor the father's serum agglutinated the group IV cells which were agglutinated by the group III<sub>1</sub> serum. The

father's cells (group IV) were not agglutinated by the group III<sub>1</sub> serum. The brother's and the sister's blood were typical group III and II, respectively; neither their serums nor cells showed unusual reactions.

TABLE 3.—*Summary of Atypical Agglutination Reactions.*

Author	Number of Cases	Subgroup of Group	Atypical Reaction Serum Agglutinates Cells
Landsteiner and Witt: Proc. Soc. Exper. Biol. & Med. <b>21</b> : 389, 1924; J. Immunol. <b>11</b> : 221, 1926	2	I	All I, 75% II
Wiener: Deutsches Arch. f. klin. Med. <b>156</b> : 305, 1927 .....	?	I	Yes
Lauer: Ztschr. f. d. ges. gericht. Med. <b>11</b> : 264, 1928 .....	?	I	Yes
Thomsen: Ztschr. f. Immunitätsforsch. u. exper. Therap. <b>57</b> : 301, 1928.....	4	I	?
Landsteiner and Levine: J. Immunol. <b>17</b> : 1, 1929	1	I (A <sub>1</sub> B)	All IV and II <sub>2</sub>
	1	I (A <sub>1</sub> B)	All IV and some II <sub>2</sub>
	1	I (A <sub>2</sub> B)	Some II <sub>1</sub> and all I (A <sub>2</sub> B)
Brem: J. A. M. A. <b>67</b> : 190 (July 15) 1916.....	1	II	Not I
Unger: J. A. M. A. <b>76</b> : 9 (Jan. 1) 1921.....	1	II	IV
Sucker: Ztschr. f. Hyg. u. Infektionskrankh. <b>102</b> : 482, 1924 .....	1	II	II and I, not III
Thomsen: Ztschr. f. Immunitätsforsch. u. exper. Therap. <b>57</b> : 301, 1928.....	19	II	?
Landsteiner and Levine: J. Immunol. <b>17</b> : 1, 1929	1	II	Not III
	3%	II	12% II
	1	II <sub>1</sub>	Some IV
	1	II <sub>2</sub>	II <sub>1</sub>
	4	II	Some IV and II
Meleney and co-workers: Am. J. M. Sc. <b>154</b> : 733, 1917 .....	Occ.	III	Not II
Sucker: Ztschr. f. Hyg. u. Infektionskrankh. <b>102</b> : 482, 1924 .....	1	III	Not II and I
Guthrie and Huck: Bull. Johns Hopkins Hosp. <b>34</b> : 37, 80 and 128, 1923.....	4	III	Not all II
Thomsen: Ztschr. f. Immunitätsforsch. u. exper. Therap. <b>57</b> : 301, 1928.....	3	III	?
Meyer and Ziskovín: Med. Klin. <b>19</b> : 87, 1923....	1	III	III
Landsteiner and Levine: J. Immunol. <b>17</b> : 1, 1929	2%	III	6% III
	6	III	Some III and IV
Ottenberg and Johnson: J. Immunol. <b>12</b> : 35, 1926 .....	1	III	Some III and IV
Wilhelm and Osgood (1932).....	1	III	Some III and IV
Beck: Ergebn. d. inn. Med. u. Kinderheilk. <b>30</b> : 150, 1926 .....	1	III	Some IV
Coca and Klein: J. Immunol. <b>8</b> : 477, 1923.....	1	IV	I after absorption with II and III cells
Unger: J. A. M. A. <b>76</b> : 9 (Jan. 1) 1921.....	6	IV	Some IV
Phillips: M. J. Australia <b>1</b> : 429, 1928.....	1	IV	Some IV
Landsteiner and Levine: J. Immunol. <b>17</b> : 1, 1929	5%	IV	10-20% IV
Thomsen: Ztschr. f. Immunitätsforsch. u. exper. Therap. <b>57</b> : 301, 1928.....	6	IV	?
	2	IV	Not III
	1	IV	Not II

In table 3 are summarized the subgroups which have so far been recognized. Note that the case of Meyer and Siskovín and the case of Beck, while incompletely studied, probably belong to the same subgroup as the case here reported. Ottenberg and Johnson have reported one case and Landsteiner and Levine six cases (disregarding the ±

reactions) which seem identical with our case. The case of Ottenberg and Johnson is unique in that a fatality resulted when a group III recipient was transfused with blood from a group III donor whose serum agglutinated the recipient's cells. Landsteiner and Levine<sup>1</sup> have studied the heredity of the agglutinable properties of red cells to exceptional serums and find there is an inheritance of such properties and racial differences in their distribution.

The occurrence of subgroups is of great clinical importance, and it is surprising that texts giving the technic of the selection of donors for transfusions seldom mention the errors which may result from the occurrence of subgroups. By using this group III<sub>1</sub> serum for typing, some group IV bloods were classed as group II and some group III bloods were classed as group I. Fatal accidents would certainly have occurred had not direct matchings been done in addition. A fatal accident would be likely to occur if our subject were to be given a transfusion with blood from certain group IV (universal) donors, or even if she were a donor or recipient in a transfusion with another person in her own group.

The precautions necessary to avoid such accidents are evident. Both typing and direct matching should always be carried out. Serum selected for use in typing should be tested against a number of cell suspensions from each of the blood groups to be certain that it has a high titer and gives no atypical agglutination. When direct matching of bloods supposedly from the same group gives agglutination, the serums should be tested with cell suspensions from each group. Universal donors should not be used without direct matching of the recipient's serum with the donor's cells.

#### SUMMARY

1. A subgroup of group III is described which is characterized by a serum which agglutinates 33 per cent of group III cells and 47 per cent of group IV (Moss) cells, and by cells which are agglutinated by 43 per cent of group III serums.

2. Previously reported subgroups are summarized.

3. Precautions necessary to prevent accidents are outlined.

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1. Landsteiner, K., and Levine, P.: On the Inheritance and Racial Distribution of Agglutinable Properties of Human Blood, *J. Immunol.* **18**:87, 1930.

# CLINICAL SIGNIFICANCE OF LATENT PULMONARY TUBERCULOSIS

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A significant advance in knowledge of tuberculosis has come from recognition of the occurrence of grave, often progressive, disease that has not undermined health, has produced no evident symptoms and is unassociated with physical signs demonstrable by the usual methods of physical examination. Nevertheless, the fundamental importance of this latent tuberculosis as a forerunner of clinically manifest disease is not universally accepted. Many clinicians have been unwilling to admit that progressive tuberculous lesions are evident in roentgenographic films before the disease has produced any symptoms or physical signs. Roentgenographic examination often reveals the anatomic characters of tuberculous lesions before they have produced any functional disturbances demonstrable by existing methods. Progress in the early diagnosis of pulmonary tuberculosis by means of procedures available today is chiefly dependent on wider recognition of the value of technically adequate roentgenographic examination of the chest.

Some clinicians and roentgenologists find it difficult to separate latent from arrested tuberculosis because the lesions concerned may be indistinguishable by their anatomic characters as defined by x-ray films. Inquiry will usually determine if there have been symptoms of respiratory disease referable to pulmonary tuberculosis. The distinction between latent and arrested tuberculosis has obvious significance from the point of view both of the patient and of public health.

In 1926, we<sup>1</sup> described the numerous latent tuberculous lesions that we observed in members of families living in contact with tuberculosis and the occasional lesions found in those with no history of contact with the disease. In the present publication we describe instances of latent pulmonary tuberculosis many of which have been observed during from six to eight years.

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From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.  
1. Opie, E. L., and McPhedran, F. M.: *Am. Rev. Tuberc.* **14**:347, 1926.

In the following classification of latent tuberculous lesions of the lungs are enumerated those that are distinguishable by roentgenographic examination of the chest:

Latent tuberculous lesions of the lung (of first infection or childhood type)

- (a) Soft (appearing as spots or as flocculent shadows)
- (b) Strandlike (healing or healed)
- (c) Calcified nodules of the lung (healing or healed)

Tuberculosis of tracheobronchial lymph nodes

- (a) Massive caseous tuberculosis
- (b) Calcified tuberculosis (healing or healed)

Latent apical tuberculosis (of reinfection or adult type)

- (a) Scant lesions appearing below the posterior part of the second rib
- (b) Lesions occupying approximately one half or more of the apex above the clavicle as seen in x-ray films
- (c) Lesions extending from above below the clavicle and not exceeding those of minimal tuberculosis
- (d) Lesions equivalent in extent or character to those of moderately advanced tuberculosis

It is noteworthy that in the classification are defined the lesions recognizable with present methods in x-ray films, and to avoid controversial questions no attempt is made to define exactly the pathologic picture of the lesions concerned.

#### TUBERCULOUS INFILTRATION OF FIRST INFECTION OR CHILDHOOD TYPE

Early lesions of the parenchyma of the lung referable to tuberculous infiltration cast shadows on the roentgenographic films that occur in spots and cause a clouded or flocculent appearance (soft infiltration). In films of the chest the density of spots and their proximity to one another are rough indexes of invasion of air-containing alveolar, by solid tuberculous, tissue. Patches of tuberculous pneumonia or confluent tubercles produce similar shadows in roentgenographs of excised tuberculous lungs. Opaque, homogeneous shadows of considerable extent indicate solidification of lung tissue referable to a pneumonic process. Roentgenographic studies have emphasized the frequency with which extensive tuberculous infiltration of the lung in children undergoes resolution with complete disappearance of homogeneous density or its replacement by strandlike shadows that represent fibrous tissue. Hence, tuberculous lesions in young children usually appear as soft spots, whereas in older children they are strandlike. The transition from the former to the latter is frequently observed (table 1).

Strandlike infiltration was not found in any of the Negro children at the time when they first came under observation.

Latent infiltration of the lung that was seen as soft spots in the films of the chest of white children became clinically manifest tuberculosis within an average period of seven months after its recognition, the shortest being two weeks and the longest one year and three months. The disease was arrested in all of these seven cases after an average

TABLE 1.—*Latent Tuberculous Infiltration of the Lung of First Infection or Childhood Type*

	Age	Number With Infil- tration When First Seen	Number That Later Became Strandlike and Developed		Number That Developed into Clinically Manifest Pulmonary Tuberculosis	Per Cent That Developed into Clinically Manifest Pulmonary Tuberculosis
			No Recogniz- able Calcifi- cation of Tracheobron- chial Lymph Nodes	Recogniz- able Calcifi- cation of Tracheobron- chial Lymph Nodes		
White						
Soft infiltration	0-4	11	2	6	2	35
	5-9	6	3	..	1	
	10-14	3	3			
	15-19					
	20+					
Soft infiltration with massive caseous tuberculosis of tracheobronchial lymph nodes	0-4	2	..	1	1	
	5-9					
	10-14					
	15-19					
	20+					
Soft infiltration with calcified tracheobronchial lymph nodes	0-4	2	..	1	1	
	5-9	6	..	4	2	
	10-14					
	15-19					
	20+					
Strandlike infiltra- tion with or with- out calcified tracheobronchial lymph nodes	0-4					36.4
	5-9	3				
	10-14	3				
	15-19	1				
	20+	1				
Negro						
Soft infiltration	0-4	2	2			
	5-9					
	10-14	1				
	15-19					
	20+	1	1			
Soft infiltration with massive caseous tuberculosis of tracheobronchial lymph nodes	0-4	2	..	1	1	
	5-9	1	..	..	1	
	10-14					
	15-19	1	..	..	1	
	20+					
Soft infiltration with calcified tracheobronchial lymph nodes	0-4	1	..	1		
	5-9					
	10-14	1				
	15-19	1	..	..	1	
	20+					

period of three years and six months (minimum two years; maximum, five years and a half) following recognition of the lesion.

After recognition of similar lesions in Negro children, clinically manifest tuberculosis made its appearance after an average period of four months (least one month and greatest six months). Death occurred in one instance seven months after the lesion was first discovered. The three remaining children were under observation from

eleven months to two years and eight months, and the disease was still present. Hence, the transition to clinically recognizable disease occurs more rapidly, and the probable outcome is more unfavorable, in Negroes than in white persons.

In nineteen instances in white children, latent infiltration represented in roentgenographs by soft spots later diminished in extent and assumed a strandlike character in the film. This change was observed after an average period of two years and three months. In five instances the infiltration was accompanied by recognizable calcified tuberculosis of tracheobronchial lymph nodes when first seen, and in six more calcification of lymph nodes had made its appearance at the time when the infiltration had become strandlike.

In Negroes, soft infiltration had assumed a strandlike character in five instances after an average period of two years and three months. In one of these cases massive caseous tuberculosis became calcified and in another calcification of tracheobronchial lymph nodes became evident in the film, although during the preceding caseation the nodes had not been large enough to be demonstrable by the x-rays.

With the transition of soft spots or flocculent shadows into inconspicuous strands with or without manifest disease, it is evident that the tuberculous lesion has undergone more or less resolution. The following are examples of extensive resolution demonstrated by roentgenographic films:

Catherine, a white girl, aged 11 months, was exposed to tuberculosis in her mother, who had tubercle bacilli in her sputum. When the child was first seen there was consolidation of the lower part of the right upper lobe varying in density over an area 3.5 cm. across. After nine months the area of consolidation was only 2.5 cm. across, and there was calcification in spots (McPhedran,<sup>2</sup> fig. 5). After an additional four years and three months, a few strands and some calcified spots replaced the former opacity.

Angelina, a white girl, aged 1 year, was exposed to pulmonary tuberculosis in her mother, who had tubercle bacilli in her sputum. There was a homogeneous opaque consolidated area occupying the upper part of the left upper lobe, 4 by 3 cm. After six months cough appeared; the density of consolidation had evidently diminished, and scattered light spots were seen over the same area. After an additional one year and four months, symptoms had disappeared and the lesion was reduced to a calcified nodule and a few strands. A lymph node at the hilus of the lung had undergone calcification. Finally, after a year more the roentgenogram showed light strands and a calcified nodule in an area 3 cm. across together with a large calcified tracheobronchial lymph node.

The observations that have been cited show that homogeneous tuberculous consolidation may gradually resolve and its shadow diminish in the film so that a few strandlike markings, presumably caused by newly

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2. McPhedran, F. M.: *Am. Rev. Tuberc.* **20**:532, 1929.



formed fibrous tissue, with occasionally a few calcified spots, alone remain as scars of the healed lesion. In some instances roentgenographs show that calcification, presumably of caseous foci, has simultaneously occurred in adjacent lymph nodes.

Strandlike infiltration of the lung was found at the first roentgenographic examination in eight instances in white persons (table 1) and in no instances in Negroes. In thirty white persons with soft infiltration, the lesion became strandlike in twenty-six (86.7 per cent), in seven of whom clinically manifest tuberculosis developed that was later arrested. In eleven Negroes, soft infiltration became strandlike in five (45.5 per cent), and in none of these was tuberculosis clinically manifest.

#### MASSIVE CASEOUS TUBERCULOSIS OF TRACHEOBRONCHIAL LYMPH NODES

Caseous lesions of lymph nodes are recognizable only when they are associated with such massive enlargement that some part of the oval outline of the node is clearly recognizable against the pulmonary field either at one side of the mediastinum or in the hilus of one or the other lung. Small caseous foci are not recognizable in roentgenographic films until they have been impregnated with calcium salts.

Massive caseous tuberculosis of lymph nodes was recognized in association with clinically manifest pulmonary tuberculosis in three white persons, two of whom died, and in ten Negroes, three of whom died. Of the latter, three others had far advanced tuberculosis when last seen.

Table 2 contains all instances of latent massive caseous tuberculosis of tracheobronchial lymph nodes that were recognized. It shows that latent massive caseous tuberculosis has grave significance. In five instances it was associated with tuberculous infiltration of the lung, and in three of these, clinically manifest disease later developed. Of six instances in which massive caseous tuberculosis of tracheobronchial lymph nodes was unaccompanied by other lesions when first seen, clinically manifest pulmonary tuberculosis made its appearance in two. We have obtained no evidence that the tuberculous lesions of the lymph nodes produce recognizable symptoms or physical signs.

The lesion of the lymph nodes underwent calcification in four instances.

Massive caseous tuberculosis of tracheobronchial lymph nodes has occurred more frequently in Negro than in white children, and in the former it is evidently more likely to appear in adolescence. During the period of the present study, massive caseous tuberculosis accompanied clinically manifest tuberculosis in thirteen instances. Of these,

three were in white persons, aged 2 months, 10 and 20 years, respectively, and ten were in Negroes from 7 months to 33 years of age, seven being 12 or more years of age.

# TUBERCULOSIS OF TRACHEOBRONCHIAL LYMPH NODES WITH CALCIFICATION

To obtain information concerning the potential significance of tracheobronchial tuberculosis with calcification of the lesion, it is essential to separate instances of tracheobronchial tuberculosis unaccom-

TABLE 2.—*Latent Massive Caseous Tuberculosis of Tracheobronchial Lymph Nodes*

	Sex	Age When First Seen, Years	Associated Pulmonary Lesion When First Seen	Subsequent Change in Lymph Nodes	Subsequent Change in Pulmonary Lesion	Comment
<b>White</b>						
803,R	F	3	Soft infiltration	Calcified	Strands	
787,M	F	4 3/12	Soft infiltration	.....	Manifest pulmonary tuberculosis	
954,A	M	15	.....	.....	.....	One examination only
<b>Negro</b>						
891,G	M	1 7/12	Soft infiltration	.....	Manifest pulmonary tuberculosis	Observed one week only
828,H	F	4	Soft infiltration	.....	Manifest pulmonary tuberculosis	Died
124,G	M	6	Soft infiltration	Calcified	Strands	
737,V	F	7	.....	Calcified		
281,T	F	9 7/12	.....	.....	Manifest pulmonary tuberculosis	
941,C	F	12	.....	Calcified		
896,N	F	12	.....	.....	.....	One examination only
221,R	F	15	.....	.....	Manifest pulmonary tuberculosis	

panied by pulmonary lesions from those in which at the first observation the tracheobronchial tuberculosis is associated with latent infiltration of the lung substance of either first infection (childhood type) or of reinfection (latent apical or adult type). We have no evidence that partially or completely calcified lesions of tracheobronchial lymph nodes produce recognizable symptoms or physical signs.

Table 3 shows the frequency with which clinically manifest pulmonary disease developed in persons with calcified tracheobronchial tuberculosis with and without pulmonary lesions. In persons with tracheobronchial tuberculosis recognized by the presence of calcification, clinically manifest disease develops only in a small percentage of cases. When the lesion was associated with no recognizable infiltration of the

lung, the incidence of subsequent manifest tuberculosis was 1.8 per cent in white people, and 3.1 per cent in Negroes. In all save one of these instances the disease made its appearance in persons in contact with a patient with tuberculosis with tubercle bacilli in the sputum. When tracheobronchial tuberculosis with calcification is accompanied by infiltration of the lung, the percentage of those who develop clinical tuberculosis is much greater and approximates that following infiltration

TABLE 3.—Frequency with Which Persons with Latent Tuberculosis of Tracheobronchial Lymph Nodes Develop Clinically Manifest Tuberculosis

Lesion When First Seen		Age, Years	Number with Tracheo-Bronchial Tuberculosis	Number That Changed to Clinically Manifest Tuberculosis	Per Cent That Changed to Clinically Manifest Tuberculosis
White	Calcified tracheobronchial tuberculosis alone	0-4	17	1	1.8
		5-9	52	0	
		10-14	76	2	
		15-19	26	..	
		20-39	47	1	
		40+	18	..	
	Calcified tracheobronchial tuberculosis with infiltration of first infection	0-4	3	1	23.1
		5-9	7	2	
		10-14	2	..	
		15-19	1	..	
		20-39	..	..	
		40+	..	..	
	Calcified tracheobronchial tuberculosis with latent apical tuberculosis	0-4	..	..	18.7
		5-9	..	..	
		10-14	3	1	
		15-19	4	1	
		20-39	9	1	
		40+	12	..	
Negro	Calcified tracheobronchial tuberculosis alone	0-4	..	..	3.1
		5-9	8	..	
		10-14	10	..	
		15-19	5	1	
		20-39	9	..	
		40+	6	..	
	Calcified tracheobronchial tuberculosis with infiltration of first infection	0-4	1	..	
		5-9	..	..	
		10-14	1	..	
		15-19	1	..	
		20-39	..	..	
		40+	..	..	

Note.—There were no instances in which Negroes with calcified tracheobronchial and associated latent apical lesions developed clinically manifest disease.

with no demonstrable tracheobronchial lesion. The frequency with which those with tracheobronchial tuberculosis and latent apical lesions develop clinically manifest disease is also much greater (18.7 per cent) than when only tracheobronchial lesions occur and closely approximates the figure for all latent apical lesions (20 per cent).

LATENT APICAL TUBERCULOSIS

Latent apical lesions have been divided into the following groups defined by their anatomic extent in order to measure their potential significance:

1. Definite but scant lesions seen immediately below the lower border of the posterior part of the second rib.

2. Well defined lesions occupying approximately half or more of the apex above the clavicle. It is assumed that in the roentgenograph the shadow of the mesial part of the clavicle lies on that of the posterior part of the fourth rib.

3. Lesions extending from above below the clavicle and not exceeding those of clinically manifest minimal tuberculosis, that is, limited to the pulmonary field above the level of the upper margin of the second chondrosternal junction and the fifth vertebral spine. When a cavity or dense consolidation is present, the lesion is placed in group 4.

TABLE 4.—*Frequency with Which Persons of Various Ages with Latent Apical Tuberculosis Have Developed Clinically Manifest Tuberculosis*

	Extent of Lesion	Age	Number With Latent Apical Lesions	Number That Developed Manifest Tuberculosis	Per Cent That Developed Manifest Tuberculosis
Group 1:	Scant lesions	10-14	6	2	5.7
		15-19	4	0	
		20-39	25	0	
		40+	6	0	0.0
Group 2:	Approximately half or more of apex above clavicle	10-14	7	3	25.0
		15-19	8	2	
		20-39	17	3	
		40+	16	1	6.2
Group 3:	Equivalent to minimal tuberculosis	10-14	1	0	47.8
		15-19	11	7	
		20-39	11	4	
		40+	12	1	8.3
Group 4:	Equivalent to moderately advanced tuberculosis	10-14	2	1	50.0
		15-19	1	1	
		20-39	3	1	

4. Moderately advanced latent lesions occupying an area exceeding that just defined and equivalent to moderately advanced, clinically manifest tuberculosis.

In view of the varying character of tuberculous infection at different ages, latent lesions have been grouped by age (table 4) in order to determine the frequency with which manifest tuberculosis makes its appearance in each age group.

Table 4 shows that latent apical lesions more frequently develop into manifest disease before than after 40 years of age. After this age latent lesions appear to have assumed a considerable degree of stability, although in a small proportion of cases (approximately 6 per cent) the disease previously latent becomes manifest. The table further shows that in persons between 10 and 40 years old, the probability that the lesion will seriously impair health increases with its extent at the time of observation. Of the smallest recognizable lesions (group 1) only a

few (5.7 per cent) develop into clinically manifest disease, whereas of more conspicuous lesions, limited to the apex above the clavicle, one fourth develop into clinically recognizable disease. Of all lesions that extend below the clavicle, approximately one half become manifest, and the potential significance of this lesion is evidently so great that it should receive the same treatment as clinically manifest tuberculosis until repeated roentgenographic examination has demonstrated that it is not progressive.

The average time between the discovery of latent apical tuberculosis and the development of clinically manifest disease was approximately one year and four months, the longest time being five and a half years, and the shortest, two months.

In seven of the twenty-six persons whose latent apical lesion became manifest disease, tubercle bacilli appeared in the sputum, and five died.

The number of latent apical lesions in Negroes has been so small that tabulation of them has been omitted. The total number was fourteen, and in two of them clinically manifest tuberculosis developed. These two patients when first seen had lesions of groups 2 and 3.

#### CONCLUSIONS

The early diagnosis of pulmonary tuberculosis is in a large part dependent on the recognition of lesions that have not impaired health (latent pulmonary tuberculosis).

Soft infiltration of the lung referable to a first infection with tuberculosis (childhood type) in approximately two thirds of all instances undergoes resolution and healing with formation of a fibrous or calcified scar and is accompanied by no evident symptoms or physical signs, but in 35 per cent of cases clinically manifest tuberculosis makes its appearance. In white children this disease usually becomes arrested, but in Negro children it more frequently pursues an unfavorable course.

Massive caseous tuberculosis of tracheobronchial lymph nodes is infrequently recognizable in roentgenographs, and when not associated with demonstrable pulmonary infiltration is seldom if ever accompanied by demonstrable symptoms or physical signs; with obvious development of a pulmonary lesion, it is followed by clinically manifest pulmonary tuberculosis in about one third of the cases. It is found oftener in Negroes than in white persons, and in the former occurs more frequently during adolescence.

Tracheobronchial lymph node tuberculosis with recognizable calcification is with few exceptions a healed or healing lesion, and its recognition if unaccompanied by tuberculous infiltration of the lung when first seen is seldom (in only 2 or 3 per cent of cases) followed by manifest pulmonary disease.

The potential significance of latent apical tuberculosis varies with age and the anatomic extent of the lesion. After 40 years of age these lesions are usually stationary.

In younger persons scant lesions projecting below the border of the second posterior rib are followed by clinically manifest tuberculosis in approximately 6 per cent of instances.

Of latent apical lesions that occupy approximately one half or more of the apex above the level of the clavicle, one fourth develop into clinically manifest disease.

Of latent apical lesions that extend from above below the clavicle, approximately half become clinically manifest tuberculosis.

Persons less than 40 years of age with latent apical lesions scattered over an area approximating one half of the apex above the clavicle or with more extensive lesions, even though they are in apparently good health, should receive the treatment of clinically manifest pulmonary tuberculosis until repeated roentgenographic examinations have shown that the lesion is not progressive.

# FUNCTION OF THE LIVER

## AN APPRAISAL OF THE MODIFIED DEXTROSE TOLERANCE TEST

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In 1930, Althausen, Gunther, Lagen and Kerr<sup>1</sup> described a modified dextrose tolerance test, which they offered as an index of the metabolic function of the liver. The technic of this test, performed on patients who had been for several days on a regular hospital diet, was as follows:

1. Estimation of blood sugar during fasting was made in the morning.
2. The patient was then given 20 units of insulin.
3. Twenty minutes later, the patient was given 50 Gm. of dextrose in 500 cc. of water by mouth, followed by 1,000 cc. of water by mouth.
4. Blood sugar determinations were made at one-half hour, one hour, two hours and three hours after the ingestion of the dextrose and water.

These authors observed that in ten patients without evidence of hepatic disease, the average of the blood sugar curves resulting from this test at no time fell below the fasting level, but that in patients who gave clinical evidence of hepatic insufficiency, there was a terminal fall in blood sugar to a point considerably below the fasting level, often accompanied by symptoms of hypoglycemia. This test was based on the hypothesis that "in normal persons the dextrose ingested during the test seems to be polymerized to glycogen, and in return released as dextrose with sufficient rapidity to counteract impending hypoglycemia, whereas in patients with hepatic disease, this process is sufficiently slowed to permit of reaching abnormally low blood sugar levels." They placed the dividing line between normal and abnormal responses at 70 mg. of sugar per hundred cubic centimeters of blood. They tested sixty-four patients and found, after eliminating certain cases which were unsatisfactory because of complications, that there was a 91 per cent agreement between the modified dextrose tolerance test and the rose bengal dye test of hepatic function.

In 1931, the senior author, Althausen,<sup>2</sup> reported the application of this test, together with the rose bengal test, in five cases of toxic

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1. Althausen, T. L.; Gunther, L.; Lagen, J. B., and Kerr, W. J.: Modification of the Dextrose Tolerance Test as an Index of the Metabolic Activity of the Liver, *Arch. Int. Med.* **46**:482 (Sept.) 1930.

2. Althausen, T. L.: Functional Aspects of Regenerated Liver Tissue, *Arch. Int. Med.* **48**:667 (Oct.) 1931.

cirrhosis of the liver. In three of these cases the diagnosis was proved by autopsy or biopsy. In all instances in which the determinations were made in the chronic stage of the disease, he found by this means a normal carbohydrate metabolism in the face of marked retention of the rose bengal dye in the blood stream. Since in the first paper a close correlation between the carbohydrate and the dye tests had apparently been demonstrated in other forms of hepatic disease, it was concluded that the discrepancy between these tests in toxic cirrhosis constituted a basis for the clinical diagnosis of this disease. The simultaneous occurrence of normal hepatic carbohydrate metabolism and marked impairment of excretory function may be explained, says the author, by the pathologic anatomy and physiology of toxic cirrhosis. Anatomically, this condition is characterized by isolated nodules and areas of regenerated, usually bile-stained hepatic parenchyma. These areas, because they consist of normal cells and possess an adequate blood supply, are able to carry on carbohydrate metabolism in a normal fashion, but because they have no connection with the biliary tree, they are unable to perform the normal excretory functions.

In a critical review of these contributions, it is hard to escape the conclusion that the validity of the modified dextrose tolerance test in hepatic disease of any nature depends entirely on the question of whether or not persons with normal livers always respond to the test in the same way—i. e., by the maintenance of the blood sugar throughout the procedure at a level above 70 mg. per hundred cubic centimeters (the critical level as given by Althausen and his collaborators). The present study was undertaken in an attempt to answer this question conclusively.

#### METHODS

The modified dextrose tolerance test was performed on fourteen subjects. Of these, four were considered unquestionably normal so far as the liver was concerned; six gave a history suggesting possible damage to the liver at some earlier date, but presented at the time of examination no symptom or sign of hepatic disease, and four gave frank evidence of an existing hepatic pathologic process. The concern of this paper lies chiefly in the normal and probably normal cases, but the abnormal have been included as a matter of interest.

The technic followed in the test was identical with that used by Althausen, Gunther, Lagen and Kerr.<sup>1</sup> For several days prior to the test the patients had been either on a regular hospital diet or, because of the nature of the particular illness, on a special diet, both of which contained from 250 to 300 Gm. of carbohydrate. At 9:00 a. m., with the patient in a fasting condition, blood was drawn for the determination of sugar. At 9:10, the patient was given 20 units of insulin hypodermically. At 9:30, the patient ingested 50 Gm. of dextrose in 500 cc. of water, followed by 1,000 cc. of water. Samples for blood sugar determinations were drawn at 10:00, 10:30 and 11:30 a. m., and at 12:30 p. m. If signs or symptoms of hypoglycemia supervened at any time; a sample of blood was



taken, and the test was immediately terminated by the administration of orange juice and sugar by mouth.

The samples of blood sugar were in practically all instances transferred at once to the chemical laboratory, where analysis was begun before intrinsic chemical changes might occur. The analyses, made through the courtesy of Dr. Dorothy Gaston, were based on the method described by Folin in 1929 for determining blood sugar<sup>3</sup> and on the tungstate sulphate filter method,<sup>4</sup> determinations being made on the unclaked blood filtrate. Emphasis should be laid on the fact that, because some of the nonsugar-reducing substances are eliminated, the values for blood sugar obtained by these methods are lower than those given by the older analytic procedures, normal values being from 60 to 90 mg. per hundred cubic centimeters. Seventy milligrams per hundred cubic centimeters was the critical level decided on by Althausen and his co-workers, below which hypoglycemia was considered to exist. This is about 10 points below the lower limit of normal blood sugar as considered by most authors (80 mg.).<sup>5</sup> In order that the results here presented may be compared with those under discussion, a value 10 points below the lower limit of the normal (60 mg.) as given by the newer method of analysis has been chosen, giving a critical level of 50 mg. That this figure is not too high is borne out by the fact that all patients showing blood sugar of less than 50 mg. per hundred cubic centimeters exhibited signs and symptoms of hypoglycemia, such as hunger, pallor, sweating, drowsiness and tachycardia.

Because of the lack of agreement among various authors as to the value of dye tests of hepatic function, it was not deemed worth while to perform these in the normal and "probably normal" cases. The bromsulphalein intravenous dye test was done only in the four cases of outspoken disease of the liver. As has been pointed out, these cases are included here as a matter of interest, and for the sake of comparison, the main issue being the response of persons without hepatic disease to the modified dextrose tolerance test.

#### DATA

The accompanying table and chart are divided into three groups. Group I includes those cases in which no evidence of hepatic disease could be obtained from the history or from physical examination. All these patients were being treated for functional disorders of the gastro-intestinal tract, and in none was there any evidence of organic disease. In case 1, the modified dextrose tolerance test gave indeterminate results. Because the patient complained of "feeling queer" and had a cold, clammy skin at the end of two hours, the test was prematurely terminated, although the blood sugar did not fall below 55 mg. All the other patients of this group experienced a decided drop in blood sugar, and presented unmistakable clinical manifestations of hypoglycemia.

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3. Folin, Otto: Two Revised Copper Methods for Blood Sugar Determination, *J. Biol. Chem.* **82**:83 (April) 1929.

4. Folin, Otto: Unclaked Blood as a Basis for Blood Analysis, *J. Biol. Chem.* **86**:173 (March) 1930.

5. McClellan, W. S., and Wardlaw, H. S. H.: Hypoglycemic Reactions Following Glucose Ingestion, *J. Clin. Investigation* **11**:513 (May) 1932.

# Summary of Clinical Data and Tests of Hepatic Function

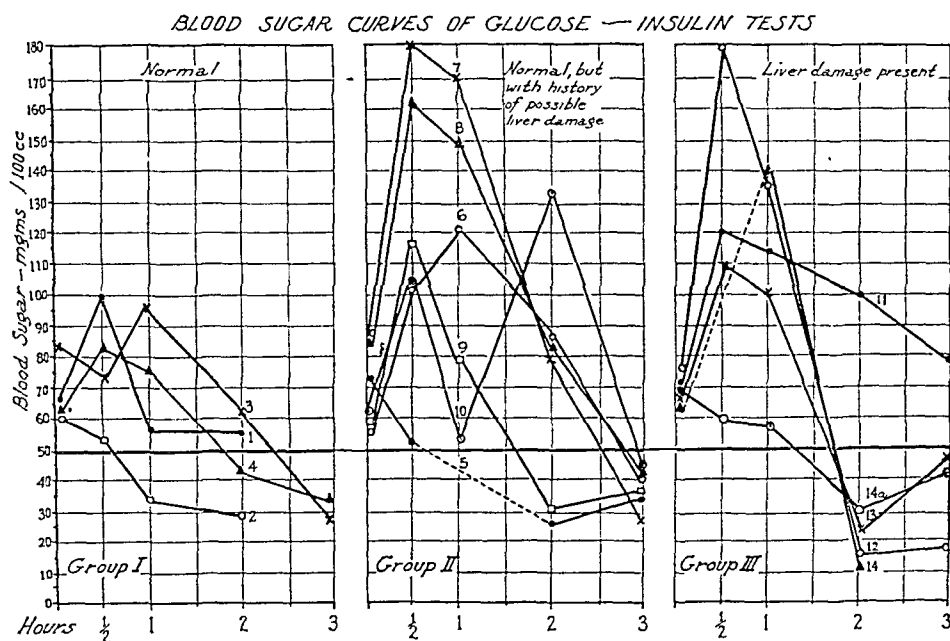
Case Number	Age	Sex	Diagnosis	Significant Physical Findings	History of Possible Hepatic Damage	Dextrose-Insulin Test * age of Dye Re- tained					Percent- age of Dye Re- tained	Comment
						Blood Sugar						
						Shock F	$\frac{1}{2}$ Hr.	1 Hr.	2 Hr.	$\frac{3}{4}$ Hr.		
GROUP I												
1	46	F	Chronic functional colitis	General abdominal tenderness	None	?	66	99	57	55	..	..
2	30	F	Malnutrition; chronic functional colitis	None	None	+	61	53	34	28	..	..
3	29	F	Cardiospasm	None	None	+	83	73	96	67	27	..
4	56	F	Migraine; cathartic colitis	None	None	+	63	83	75	42	33	..
GROUP II												
5	27	F	Chronic functional colitis; nervous vomiting	Highly nervous; abdominal scars; general abdominal tenderness	Cholecystectomy at 19	+	73	52	..	25	34	..
6	34	F	Chronic sinusitis; chronic cystitis and pyelitis	None	1 glass port.wine daily	0	55	102	122	85	40	..
7	58	M	Duodenal ulcer with moderate stenosis; inactive pulmonary tuberculosis	Nervousness; subcapsular rales; lower abdominal and epigastric tenderness	Painless jaundice at 32	+	85	181	169	82	20	..
8	44	M	Duodenal ulcer	Abdominal scars	Cholecystectomy; no jaundice	+	85	162	148	84	42	..
9	23	M	Duodenal ulcer with moderate stenosis	Cardiac systolic murmur; epigastric tenderness and tenderness in right lower quadrant	Alcohol at rare intervals	+	53	116	79	30	36	..

10	44	F	No organic disease	Tender right lower quadrant and right upper quadrant	Moderate pain in right upper quadrant without jaundice	+	62	102	53	133	43	..	..	Roentgenogram of gallbladder normal; blood sugar specimens at 1 hr. and 2 hrs. mixed in laboratory?
11	66	M	Carcinoma of pancreas	Jaundice; mass in right upper quadrant; enlarged firm, smooth liver; spleen not palpable	GROUP III	0	71	120	114	99	78	10-	0	Diagnosis confirmed at operation
12	52	F	Atrophic cirrhosis with jaundice; duodenal ulcer	Jaundice; liver enlarged, hard, nodular; spleen palpable; anemia		+	75	179	135	15	17	0	0	Diagnosis confirmed grossly at operation; died later of pneumonia; no autopsy
13	39	M	Syphilitic hepatitis	Slight icterus; enlarged, hard, nodular liver; enlarged, firm spleen; ascites; Wassermann and Kahn tests ++++	Alcohol at occasional intervals	+	66	109	100	23	47	10	5	Improving under antisyphilitic therapy
14	39	M	Syphilis (late) of central nervous system; arsenamine hepatitis	Jaundice; marked hepatic enlargement—soft; spleen not palpable	Arsenical antisyphilitic treatment for 1½ years; last treatment five weeks before admission	+	63	...	140	11	..	..	..	
							..	...	...	...	..	80	70	
							..	...	...	...	..	..	..	12/23/31 Re-covered
							..	...	...	...	..	..	..	12/26/31
							..	...	...	...	..	..	..	12/29/31
							..	...	...	...	..	20	10	1/ 2/32
							..	...	...	...	..	20	10	1/ 5/32
							..	...	...	...	..	..	..	1/ 6/32
							+	65	59	57	29	42	..	6/ 3/32

\* Hypoglycemic shock present, +; absent, 0; questionable, ?. Values for blood sugar are given as mg. per hundred cubic centimeters.

† The table shows the number of grams of galactose excreted in the urine during a period of five hours after the ingestion of 40 Gm. of this substance.

Group II consists of patients who gave a history of possible hepatic damage at an earlier date, but who, at the time of this study, were being treated for conditions in no recognized way related to the liver, and who gave no evidence of disease of the liver. On examination of the factors listed as possibly having produced previous hepatic injury, it seems unlikely that most of them per se could have caused serious dysfunction at any time, and even less likely that they could still be cogent in affecting any test of hepatic function. In case 5, the patient had had a cholecystectomy eight years before; in case 6, the patient was accustomed to taking one glass of port wine daily; in case 7, the patient had had painless jaundice twenty-six years before; in case 8, the patient had had a cholecystectomy with no history of jaundice; in case 9, the patient had indulged rarely in alcohol; in case 10, the patient complained of moderate pain in the right upper quadrant



Blood sugar curves obtained by dextrose-insulin tests. The horizontal line at the level of 50 mg. per 100 cubic centimeters represents the critical level for normal, below which hypoglycemia is considered to exist. Figures near curves indicate case numbers. A second determination made five months after 14 on the same patient is represented by 14a. Broken lines connect points between which one blood sugar sample was omitted.

but had never had colic or jaundice, and a roentgenogram of the gall-bladder showed normal visualization without stone. Since, however, no one can say with certainty that such factors have not produced some degree of parenchymal change, these cases are grouped separately, though it is believed that they may be classed as normal so far as intrahepatic physiology is concerned. All, without exception, showed chemical and clinical evidence of hypoglycemia.

Group III includes those cases in which frank hepatic disease was present. Jaundice and enlargement of the liver were present in all. The patient in case 11 had a carcinoma of the head of the pancreas with marked jaundice, yet showed no retention of dye in the blood stream at the end of an hour, and was the only patient who did not respond to the dextrose-insulin test by a drop in blood sugar. In case 12, the condition was diagnosed as atrophic cirrhosis of the liver and duodenal ulcer. The diagnosis was confirmed at operation. The patient was jaundiced and had an enlarged, hard, finely nodular liver, an enlarged spleen and secondary anemia. This case is of interest in that it showed marked hypoglycemia by the modified dextrose tolerance test, but no retention of bromsulphalein in the blood stream even at the end of half an hour. Althausen, in his cases of toxic cirrhosis, described exactly the opposite situation—namely, a normal reaction to the carbohydrate test and an abnormal reaction to the dye test. In case 13, in which the condition was diagnosed as syphilitic hepatitis, slight icterus, an enlarged, hard, nodular liver, a large firm spleen and ascites were present. The blood gave a positive reaction to the Wassermann and Kahn tests. This case is similar to the preceding one in showing, though to a lesser degree, a hypoglycemic reaction with an almost normal reaction to the bromsulphalein test. The patient in case 14, when first seen, about a week after the onset of jaundice induced by an arsphenamine hepatitis, had a marked retention of dye. Six days later, when the jaundice was clearing, the modified dextrose tolerance test produced a severe hypoglycemia at the end of two hours, and in the galactose test, done three days before, 8 Gm. was excreted (the normal excretion being 3 Gm. or less). Five months later, there was no retention of dye at the end of one-half hour, and 3.4 Gm. of galactose was excreted in five hours, but the modified dextrose tolerance test still showed a definite hypoglycemia (29 mg. per one hundred cubic centimeters).

#### COMMENT

It is apparent from the foregoing data that the modified dextrose tolerance test produced a terminal hypoglycemia in nine of ten patients who gave no evidence of hepatic disease. It is also clear that there is no essential difference between the response of this group and that of the group in which frank hepatic damage was present. The curve in case 9 (duodenal ulcer), for example, can be practically superimposed on that in case 13 (syphilitic hepatitis). The only distinction between the two groups is that in the cases with hepatic damage the peaks of the curves were higher, and the minimal blood sugar levels were, on the whole, somewhat lower and were reached sooner, than in most of the normal cases. No explanation for the wide variation in the

maximal blood sugar levels is apparent. Althausen noted the same phenomenon in his cases, and he also offered no explanation. This feature, however, is irrelevant to the present study. The point to be emphasized is that a definite hypoglycemia was produced in practically all patients who were considered to have normal livers, as well as in those whose livers were diseased.

Case 14, that of a patient with arsphenamine hepatitis, presents perhaps one of the strongest arguments against the validity of the modified dextrose tolerance test. This patient, who at the onset of his illness exhibited evidence of severe hepatic damage by the dye, the galactose and the dextrose-insulin tests, showed a normal reaction to the bromsulphalein test and an almost normal reaction to the galactose test five months later but still exhibited marked hypoglycemia with the modified dextrose tolerance test. Had hypoglycemia not developed in most of the normal cases, one might infer that the results in this case indicate that the modified dextrose tolerance test is more sensitive than the other tests and can detect lesser degrees of hepatic damage. In the face of the results in persons with normal livers, however, such an inference is not justified.

Results somewhat similar to those in case 14 were obtained in cases 12 and 13. The dye tests gave normal results, but the modified dextrose tolerance tests showed definite hypoglycemia, the reverse of the condition reported by Althausen as diagnostic of toxic cirrhosis. Althausen, in discussing his findings in this disease, attributed the impairment of ability to excrete dye, coincident with a normal dextrose-insulin test, to the presence of areas of regenerated liver parenchyma able to carry on carbohydrate metabolism normally, but unable to excrete dye or bile because of the absence of available bile channels. If one assumes, with Althausen, that the excretion of dye and carbohydrate metabolism are both functions of the polygonal cells of the liver, one would be justified in expecting that if in any condition there is enough hepatic parenchyma having access to the biliary system to give a normal excretion of dye, the same parenchyma should be capable of performing its normal metabolic functions as regards carbohydrates. Applying this hypothesis to cases 12, 13 and 14, one finds that there is indeed a normal excretion of dye, but that the expected normality of carbohydrate metabolism, as judged by the dextrose-insulin test, is not forthcoming. One must conclude, therefore, either that (*a*) the tests are inadequate, or (*b*) there exists some degree of differential hepatic function. The adequacy of the dye tests, as implied, is still open to question. It has already been shown, however, that the modified

dextrose tolerance test is unreliable, for hypoglycemic reactions occurred in the normal cases of this series (groups I and II) just as in the abnormal ones (group III). Consequently, although the existence of differential hepatic function is a possibility, it is not proved by the method under consideration.

From the practical point of view, therefore, it seems obvious that the modified dextrose tolerance test cannot be regarded as a satisfactory test of the metabolic activity of the diseased liver. On the same basis, there is no justification for the theory that the simultaneous presence of a "normal" modified dextrose tolerance test and an "abnormal" dye test in a person with disease of the liver indicates the existence of a toxic cirrhosis. Any attempt at differential diagnosis on such a basis is invalidated by the fact that this carbohydrate test frequently gives the same results in normal persons as in those with proved hepatic disease.

From the theoretical standpoint also, the dextrose-insulin test in its present form is open to several objections. In the first place, it is a common experience to find that in normal persons the ordinary dextrose tolerance test, in which 100 Gm. of dextrose without insulin is given, is often followed by a drop in blood sugar to a point below the fasting level. McClellan and Wardlaw,<sup>5</sup> in a review of various conditions leading to hypoglycemia, cite the ingestion of carbohydrate as one of them, and refer to the work of Folin and Berglund,<sup>6</sup> of Hamman and Hirschman,<sup>7</sup> of Foster,<sup>8</sup> of Stenström<sup>9</sup> and of John,<sup>10</sup> all of whom have reported a drop in blood sugar to below fasting levels, in some cases as low as from 31 to 45 mg., in from two to four hours after the ingestion of varying amounts of dextrose by normal subjects.

If, then, the ingestion of 100 Gm. of dextrose alone is frequently followed by hypoglycemia, it seems logical to suppose that in a test in which 20 units of insulin is given to a fasting subject and covered by only 50 Gm. of dextrose, low blood sugar levels and insulin reactions would be encountered with even greater frequency. That such is the case is borne out by the preceding studies.

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6. Folin, Otto, and Berglund, H.: Some New Observations and Interpretations with Reference to the Transportation, Retention and Excretion of Carbohydrates, *J. Biol. Chem.* **51**:213 (March) 1922.

7. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar: IV. Effects upon the Blood Sugar of Repeated Ingestion of Glucose, *Bull. Johns Hopkins Hosp.* **30**:306 (Oct.) 1919.

8. Foster, G. L.: Studies on Carbohydrate Metabolism: I. Some Comparisons of Blood Sugar Concentration in Venous Blood and in Finger Blood, *J. Biol. Chem.* **55**:291 (Feb.) 1923.

9. Stenström, T.: Hypoglykämische Reaktion nach Funktionsprobe mit Glykose, *Deutsches Arch. f. klin. Med.* **157**:216 (Oct.) 1927.

10. John, H. J.: Hyperinsulinism, *Surg., Gynec. & Obst.* **44**:190 (Feb.) 1927.

In the second place, the metabolism of dextrose is a complex process, and is susceptible of modification by a number of factors other than those directly connected with the liver. Althausen and his colleagues<sup>1</sup> mention diabetes mellitus, thyrotoxicosis, myasthenia gravis and diabetes insipidus as being conditions which should theoretically interfere with the estimation of carbohydrate metabolism. McClellan and Wardlaw,<sup>5</sup> in a review of the literature on hypoglycemia, list, among other things, physical exhaustion, renal glycosuria, idiopathic hyperinsulinism, Addison's disease, progressive muscular dystrophy, scleroderma, bronchial asthma and changes in the nervous system as conditions in which low blood sugar has been found during fasting. It is not expected that the frequency of occurrence of these abnormal states in disease of the liver would be sufficient to interfere seriously with the general adoption of the dextrose-insulin test; but the presence of hypoglycemia in these conditions reconfirms the fact, already well established, that the metabolism of dextrose and often its expression in values of blood sugar are closely linked with the function of organs other than the liver and the pancreas, especially the thyroid, pituitary and suprarenal glands, and probably the muscles. It is interesting to note in this connection that Folin and Berglund,<sup>6</sup> in 1922, during a study of the effects of the ingestion of dextrose in man, observed that the hyperglycemia so produced was augmented by the emotional reaction of a nervous subject, who fainted during a venipuncture. Emotional hyperglycemia has since become a well recognized entity, and constitutes another possible variable in any study of dextrose metabolism in man.

Finally, if one were to waive all the foregoing considerations, there would still remain the well known fact that there is a wide variation among normal persons with respect to tolerance for insulin. The response of an obese subject, for example, to a certain dose of insulin, is likely to be different from that of a malnourished one. It is possible that the modified dextrose tolerance test, based on the administration of a certain amount of dextrose and a certain amount of insulin per pound of body weight or per unit of surface area, might yield more satisfactory results than could be expected from its administration according to the present technic. This possibility, however, because of the many variable factors already mentioned, is considered to be remote.

#### SUMMARY

1. The modified dextrose tolerance test of the function of the liver, as described by Althausen, Gunther, Lagen and Kerr, was performed on ten patients who were considered to have normal livers at the time of examination, and on four patients with frank hepatic disease.



2. Of the ten normal patients, nine responded to the test by a drop in blood sugar to points considerably below the critical level for normal reactions, and showed symptoms and signs of hypoglycemia.

3. Of the four patients with frank hepatic disease, three responded by definite chemical and clinical hypoglycemia.

4. There was no essential difference between the behavior of the normal and the abnormal groups.

#### CONCLUSION

The modified dextrose tolerance test in its present form is not a satisfactory measure of the metabolic function of the liver.

## Correspondence

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### "THE RELATION OF WITHDRAWAL OF CEREBROSPINAL FLUID TO THE BODY TEMPERATURE"

*To the Editor:*—I should like to call attention to the fact that the article published by Dr. Alfred Gordon of Philadelphia, entitled, "The Relation of Withdrawal of Cerebrospinal Fluid to the Body Temperature," in the *ARCHIVES OF INTERNAL MEDICINE* (44:263 [Aug.] 1929) is, as regards comment, summary, conclusions and references, merely a condensed and slightly altered translation of my own paper entitled, "Die Beziehungen von pathologischen und experimentellen Veränderungen der physikalischen Liquorverhältnisse des Menschen zur Körpertemperatur," published in the *Zeitschrift für die gesamte Neurologie und Psychiatrie* (105:347, 1926).

Dr. Gordon has also published a similar translation, "La relation du liquide céphalo-rachidien avec la température du corps humain," in the *Revue neurologique* (2:44, 1929).

H. A. STRECKER, M.D., Birmingham, England.

*To the Editor:*—Years before Dr. Strecker's article appeared in the *Zeitschrift für die gesamte Neurologie und Psychiatrie* I became interested in the subject under discussion, as stated in the introductory remarks of my article. From the extensive references published in Dr. Strecker's article one can see how many men made observations on this subject. I kept on collecting personal cases of neuropsychiatric character until I had accumulated 250, and only then did I publish my observations. In medicine many men may work on the same problem simultaneously in different parts of the world, and they may arrive at the same conclusions. The problem of the walls of the third ventricle or, preferably, the hypothalamic area as a thermoregulatory center has been suggested time and again clinically and experimentally. My personal views on the subject ran and still run in the same direction. The case of Dr. Strecker and mine merely show a coincidence and similarity of observation. I read extensively on this subject, and among a large literature I selected only a few references, which were mentioned in my article. They happened to be among the many references which Dr. Strecker used for his article. Since my few references are the property of the entire scientific world, what is wrong if I happened to peruse them in the library? As I had decided to make a systematic study of the 250 lumbar and ventricular punctures, I devised my own method of observation as to the frequency of punctures and the registration of temperature. A careful perusal of Dr. Strecker's article will show that his method is decidedly different from mine. My conclusions, as well as those of many other authors, and those of Dr. Strecker are similar, of course, but they are not altogether identical. My fate may be the same as that of many others who have worked on the same problem. Dr. Strecker may make the same reproach to others. The tracings in my article are not identical with those in his article. Tracings were necessary, and if they remind one of those in Dr. Strecker's article, it does not make them identical. My contribution was purely a clinical one and cannot be compared with that of Dr. Strecker in extent and completeness, for the reason that he viewed not only the clinical side, but also the experimental angle. He also treated the subject of hypothermia, which I have mentioned only casually. Should it be held against me if two men from different lands happen to think alike and draw the same conclusions on the same subject even though their methods are somewhat similar?

ALFRED GORDON, M.D., Philadelphia.

## Book Reviews

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**Funktionelle Pathologie.** By Gustav von Bergmann, with the assistance of Dr. Martin Goldner. Price, 18.60 marks. Pp. 425, with 74 illustrations. Berlin: Julius Springer, 1932.

The author is the well known professor of internal medicine and director of the Second Medical Clinic of the University of Berlin. The volume is a collection and summary of his clinical work and that of a group of co-workers published in various journals, textbooks and proceedings of scientific meetings over a period of more than twenty years. He states that the points of view and conclusions may be regarded as representative of a school of modern German medicine.

The first six chapters deal with the gastro-intestinal, pancreatic and biliary systems. These are followed by a chapter each on inflammation and allergy, obesity and malnutrition and hyperthyroidism and the thyrotic constitution. Four chapters are devoted to disturbances and diseases of the vascular system. Chapter 14 contains a discussion of the visceral nervous system, and is followed by a chapter called "Diagnostic Reformation"; the latter will be discussed in more detail presently. The last three chapters are entitled, respectively, "Psychophysical Reactions," "Regulations" and "Causation and Teleology." The second chapter of this group is a consideration of the regulatory processes of the various functions of the body, such as those of temperature, blood pressure, blood sugar and acid-base equilibrium, through nervous reflexes and humoral control. The third one is in large part a philosophic dissertation on the author's attitude toward modern medicine and its future possibilities. Such entities as phthisis, carcinoma and syphilis are not discussed per se, and there was no intention that the volume should serve as a *Lehrbuch*.

Barring some interesting digressions, chiefly of a roentgenologic and therapeutic nature, the theme which permeates the major portion of this work is succinctly expressed by the title "Functional Pathology." To disturbance of function the author attributes the genesis of many symptoms, conditions and eventual disease states heretofore ascribed to pathologic states or interpreted as psychoneurotic manifestations. Invariably the surgeon or the pathologist is not able to demonstrate this functional lesion anatomically. In further illustration of this theme, some of the organs will be considered. The colon is the first in order because, from roentgenoscopic examination of the larger movements of the colon of man under both normal and abnormal conditions, von Bergmann has learned to understand dyskinesia, and so far as this organ is concerned dyskinesia may be defined as a disturbance of normal coordination of the different larger and smaller intestinal movements and of tonus, in brief, a neuromuscular disturbed action. He regards constipation, "irritable" colon, ulcerative colitis, pseudo-appendicitis and appendicitis, diverticulosis and diverticulitis as the end-results of long-standing antecedent dysfunction, either latent or active. Mucous colitis is classified as a purely allergic disease, styled bronchial asthma of the colon, the result of neuromuscular and neurosecretory (parasympathetic) excitation.

The clinical attempt to apply functional pathology consciously at the bedside had its inception in the study of gastric disorder and disease. In these two chapters on the stomach again appears von Bergmann's familiar neurogenic theory of the causation of ulcer, which, briefly stated, apart from the factors of constitutional and personal characteristics, is that a disharmony of the involuntary nervous system exists, resulting in vascular or muscular spasm, focal ischemia, capillary and venous stasis, submucosal hemorrhage and eventual erosion and ulceration of the gastric wall to a variable depth by the digestive action of the gastric juice. Von Bergmann maintains that it is now possible to demonstrate the development of an ulcer from the functional disturbances to the anatomic product, which, in his opinion, is a comparatively new conception in pathology. Jores was one of the first to conceive this, with respect to the red granular kidney as a product of the functional lesion.

hypertension. Observations on the forms of dyskinesia of the excretory ducts of the larger digestive glands (for example, the extrahepatic bile ducts, pancreatic ducts) take up two chapters, and such forms of dyskinesia are considered the basis for clinical symptoms and eventual disease.

With regard to the circulatory system the author's observations include studies of the neuromuscular behavior of the arterioles, and finally of the veins. This resulted in his "dynamic conception," namely, that hypertonus, decompensation and local vascular disturbances are the results of disturbed function. He apparently considers spasm as the primary factor in the occurrence of apoplexy, myomalacia of the heart, coronary disease, intermittent claudication and the symptom of cold fingers in older persons. On the surface, this conception might seem fantastic, but von Bergmann enlists a wealth of clinical, experimental and pathologic evidence to support it.

In addition to neural disharmony, humoral types of disharmony are recognized. The vegetatively stigmatized are understood to be those of hyperthyroid constitution. The frequency of latent disease is stressed. As a consequence, there resulted the postulate "*Abbau der reinen Organneurosen*." All this induced decisive diagnostic and therapeutic changes. In the author's opinion, the demarcation between organic and functional has disappeared. He emphasizes the point that a disturbance of function, or functional disturbance, is by no means identical with a neurotic or psychic disturbance. However, the proper consideration of normal and abnormal psychic factors is an important part of medical art.

The chapter on diagnostic reformation is largely devoted to a consideration of those diseases which in the author's opinion are not diagnosed frequently enough. These are the diseases with a background of functional disturbance, and include latent hypertension, latent circulatory decompensation, disturbances induced by small herniations through the esophageal hiatus, with or without cardiospasm, and the so-called "epiphrenal complex." To these are added: gastritis; duodenal and gastrojejunal ulcer; forms of hepatopathy, such as fatty liver, latent hepatic cirrhosis, latent cholangitis and latent cholecystopathy; subacute pancreatitis; diverticula throughout the gastro-intestinal tract, particularly those of the papilla of Vater, with resultant inflammatory disease of the extrahepatic and pancreatic ducts; latent disturbances or insufficiency of the glands of internal secretion; allergic inflammatory states involving the extremities, skin, liver, intestine, gallbladder, stomach and blood vessels, and latent infections. The common diagnoses which von Bergmann considers are too often erroneous and which should be discouraged are: those of visceral neurosis, especially of the heart and stomach; ptosis and atony of all or a portion of the organs of the digestive tract; ptosis of the kidney; intestinal spasm; painful adhesions; "rheumatic" pains and intercostal neuralgia; angina abdominis; vagotonia, and sympathicotonia.

One would think that an English translation of this volume would prove an inspiration and a challenge to every American physician. Aside from the exposition of an interesting thesis, the volume contains many instructive clinical facts, a review of much original research, descriptions of functional tests more or less unfamiliar to Americans and a number of rational and novel therapeutic hints. The chapter entitled "*Psychophysische Verhaltensweisen*" could be read profitably by every clinician and neuropsychiatrist. The author's basic conception is either right or entirely wrong, and should it prove to be the former, the work of this school might be considered as epochal in the annals of clinical medicine, as Virchow's was in cellular pathology. That all are not in accord with some of his views is evidenced by articles appearing in the current German literature. For example, Sauerbruch and his school are by no means in accord with the dicta laid down by von Bergmann and his associates concerning hiatus hernia. Sauerbruch is not ready to accept the author's conception of the epiphrenal symptom complex. However, we are inclined to agree with von Bergmann as our own experience is more or less in agreement with that of the author, particularly with reference to the incidence, roentgenoscopic phenomena and the symptomatology engendered by subdiaphragmatic hernia. Von Krecke likewise insists that complaints of the right upper abdominal quadrant may be, and frequently are, purely psychogenic

in origin. That ulcerative colitis is usually the end-result of long-standing antecedent colonic dysfunction will also be disputed by many authorities in this country. The same may be said of diverticulosis of the colon. At any rate, the volume is a brilliant and thought-provoking contribution to contemporary German medical literature.

**Hospitals and Child Health: Hospitals and Dispensaries, Convalescent Care, Medical Social Service.** Reports of the Subcommittees on Hospitals and Dispensaries, Clifford G. Grulee, Chairman; Convalescent Care, Adrian V. S. Lambert, Chairman; Medical Social Service, Ida M. Cannon, Chairman. Cloth. Price, \$2.50. Pp. 279. New York: Century Company, 1932.

This volume, which is one of the publications of the White House Conference on Child Health and Protection, presents the material secured by a number of committees which studied the particular problems of hospitals and dispensaries, convalescent care and medical social service in relation to children.

The first section of the book is devoted to the study of hospitals and dispensaries in the United States. The two chief purposes of a hospital, the care of the sick and the education of professional and lay groups, form the basis for the questionnaires that were sent to the hospitals of the United States by the committee. The results of the study are revealing and interesting. It was found that the number of hospitals in the country is more than adequate. Also, although the number of beds assigned definitely for children is not proportionate to the entire bed capacity, many of the answers to the questionnaires stated that the hospitals had room for as many children's beds as are needed, although there is no special pediatric department. However, other vital matters, such as conditions of entrance, the area served, the types of cases accepted and whether there is a special pediatric staff, were not satisfactory. The children's hospitals and special hospitals seem lacking also in many essentials. The answers to questions on dispensaries lead one to believe that there are too few dispensaries, although in the ones existing the right attitude toward the patient and the control and prevention of disease seems to be present. At the end of the section is a list of recommendations which naturally follow as a result of the study.

The second section is concerned with the reports of the subcommittee on convalescent care, a discussion of the present conditions and recommendations for what should be done. Convalescence is defined as being "that period following an attack of illness during which an individual is unable to return to what would be for him a normal routine of life and during which he does not require the constant, thoughtful supervision of a physician, and it implies that he will be able to return to his normal life if relieved of life's burdens for a reasonable length of time."

The homes now used as convalescent institutions apparently are located in proper surroundings, but the reports indicate a general inadequacy so far as fire hazards, length of stay and number of beds available are concerned. That there is financial waste when a child who might be in a convalescent bed is taking up a more expensive bed in a hospital for the acutely ill cannot be questioned. Under the suggestions of what should be done, the subcommittee offers several solutions. The necessity for specialized homes and the necessity for more interest in convalescent care by the individual physicians are among the recommendations for giving better and more complete convalescent care. Foster homes are discussed, and a workable plan is suggested by Dr. Henry Dewight Chapin, who is founder and director of the Speedwell Society of New York City. At the end of the section, tables are given which are a result of the questionnaires sent out by the subcommittee.

The section on medical social service is the longest report of the three. This study includes the amount of medical social service, where located, the interpretations of the functions of medical social service, the organization, the educational equipment, the present facilities for training the workers, the relationship of medical social service to medicine, nursing and social work and recommendations based on the findings.

The recommendations among many things emphasize the necessity of encouraging medical social service and of improving this service through a discriminating analysis of accumulated experience. The section includes extracts from discussions by persons who understand the need for the coordination of all phases in carrying out the best care of the patient.

**Poliomyelitis: A Survey Made Possible by a Grant from the International Committee for the Study of Infantile Paralysis**, organized by Jeremiah Milbank. Price, \$6. Pp. 562. Baltimore: Williams & Wilkins Company, 1932.

Jeremiah Milbank of New York in 1928 wished to contribute something as a layman to the battle against poliomyelitis. After conferences with men eminently qualified to advise and plan, the International Committee for the study of Infantile Paralysis was organized, with Dr. William H. Park as chairman. Its membership was made up of the heads of the medical departments of a number of universities and laboratories here and abroad, each of whom would be free to choose those phases of the problem in which he was most interested, but all cooperating in an effort to have the sum of their work broadly inclusive of the whole field of research in this disease. Mr. Milbank's personal interest in the work was sustained and sincere, and his financial contributions over a four year period totaled \$280,000.

The present volume summarizes all the important work done on poliomyelitis. About 8,000 references were consulted, of which a bibliography of almost 800 references is given. About 80 of these references are to papers by members of the committee. The data are presented in the following seven sections: "Historical Summary," "Etiology," "Resistance and Immunity," "Symptomatology," "Treatment," "Pathology" and "Epidemiology."

A critical review of the great mass of knowledge collected would be superfluous. A few important conclusions may be noted. In 1840 Heine was the first to establish the disease as a clinical entity. The many subsequent classifications have been modified, and the following five types are recognized: abortive, nonparalytic, sub-cortical paralytic (the usual), cerebral or encephalitic (rare) and ataxic (very rare). "Probably not more than 25 per cent of all cases of poliomyelitis that can be diagnosed develop paralysis. The case fatality is usually from 10 to 15 per cent. As practically all fatal cases are in the paralyzed group, the number surviving with paralysis is much less than 25 per cent of the total number of cases. Of the cases with paralysis a complete restitution of function will take place in a goodly number and a partial restitution in the remainder. There is, so far as we know, no danger of mental defects and there is but slight indication that the child will be more susceptible to other nervous disorders." The need for some simple, but definite and absolute, diagnostic test remains. No safe method of active immunization has yet been developed. Passive immunization yields greater promise. An addendum on page 529 calls attention to the Bradford, Pa., epidemic of September, 1932, in which, of thirteen hundred children inoculated with parental whole blood, not one contracted the disease.

Regarding etiology, it is stated that "there are some workers who, while not denying that poliomyelitis is caused by a filtrable virus, believe that this virus is only one stage in the life cycle of the agent, which appears in another stage as a pleomorphic streptococcus. No such cycle has yet been demonstrated with certainty for any of the other viruses and a very considerable amount of work has been done which in our minds is sufficient to disprove any etiological relationship between the streptococcus and poliomyelitis." (The bearing of the recent work of Kendall on this question is not discussed.) The period of incubation is at least seven days.

This volume is of inestimable value in summarizing with dependable thoroughness all present information on poliomyelitis. The great amount of time and effort which went into its preparation will mean an immense saving to all future contributors to this problem. The medical profession and the public owe a large debt of gratitude to Mr. Milbank.

**Herzneurosen und moderne Kreislauftherapie.** IX. Fortbildungs-Lehrgang in Bad Nauheim, Sept. 16-18, 1932. Published by the Physicians Association of Bad Nauheim. Price, 10 marks. Pp. 159, with 22 illustrations. Dresden: Theodore Steinkopf, 1932.

This excellent and instructive brochure is divided into three main sections: (1) the cardiac neuroses, consisting of five lectures, (2) cardiovascular therapy, comprising six contributions and (3) miscellaneous, with four discussions by eminent physicians on cardiovascular anatomy, endocarditis and heart failure, pulmonary insufficiency and its reciprocal relationship to the vascular system and the rôle of the kidney in the circulation.

The reviewer has read carefully and with pleasure and interest the fifteen lectures, and aside from those in which microscopic and other means of demonstration were utilized in explaining the data, it would indeed be difficult to decide whether one was more complete or instructive than another.

The enthusiasm of Professor Groedel for the therapeutic effects of carbon dioxide baths in quite an imposing series of cardiac and vascular diseases, including hypertension and hypertrophy, is perhaps rather surprising, but one must remember that he is connected with Bad Nauheim.

The general dietetic and special drug therapy for heart diseases is amply covered by Schloss, Rosin, Schoen and Siebeck. Their discussions are masterpieces of clarity and completeness without the tendency to become prolix. These men are conservative and up-to-date.

The pharmacology and therapy of camphor and camphor substitutes is discussed by Professor Schoen, and the relatively weak and slow absorption of camphor in the form commonly used is minutely compared with the rapid response obtained from metrazol, pyridine-carbonic acid diethyl-amide and 3-methyl-5-isopropyl 2,3-cyclohexone. The latter substance is said to be chemically similar to camphor, whereas the other two substances are entirely different. While camphor and 3-methyl-5-isopropyl 2,3-cyclohexone are insoluble in water, pyridine-carbonic acid diethyl-amide and metrazol are soluble and are adapted both to oral and to intravenous administration and have in practice performed good service in cases in which rapid central stimulation was demanded, for example, in collapse following anesthesia and severe infections, morphine and carbon monoxide poisoning, usually with suicidal intent, and following an overdose of one of the many proprietary hypnotics on the market.

The chapters devoted to the anatomy of the nervous innervation of the heart and large vessels and to the more intimate structures of the vascular walls contain points of interest which could doubtless be fully understood only by seeing the diagrams and slides. The same impression is left by reading Herzog's treatment of the problem of endocarditis; viz., it cannot be appreciated without at the same time viewing his preparations.

The kidney and its relation to the cardiovascular system are handled by Professor Becker in the final chapter of the book. The logical reasoning, together with the scientific acumen which the writer displays in marshaling his facts and in making his deductions, can be appraised only by reading the original text.

This book contains much valuable material for every one specially interested in heart diseases or in any other clinical subject in which a knowledge of cardiovascular ailments is desirable; and in what branch of clinical medicine is it not?

**Physical Chemistry of Living Tissues and Life Processes.** By R. Beutner, M.D., Ph.D., Professor of Pharmacology, School of Medicine, University of Louisville. Price, \$5. Pp. 337, with 79 figures. Baltimore: Williams & Wilkins Company, 1933.

This book, by a professor of pharmacology, fills a much-needed gap in modern biologic and medical education. Its fundamental outlook savors of Jacques Loeb and the Woods Hole of his day. It is the attempt of a biologist to apply physics and chemistry to cells. In this respect its purpose is distinctly futuristic, because the application of fundamental laws to the physiology of cells is in its beginning. Much of the volume will, no doubt, have to be rewritten as knowledge of cytologic

physics and chemistry increases. Nevertheless, the work recommends itself to the student of biology and medicine, especially to the student of experimental medicine, because its point of view is distinctly that of the coming generation.

The book introduces life "as a scientific problem" and proposes the finding of suitable artificial models for the study of phenomena peculiar to living organisms. The first section discusses membranes, electrolytes and osmosis. Permeability and body fluids are here expounded. The second section deals with surface forces and crystallization. Emulsions and artificial cells are described which exhibit ameboid movement and even respiration. The third section enumerates electrical currents in tissues. Electrode potentials and phase boundary potentials are considered in the light of action currents and the current injury. Much of this material would be termed biophysics by modern physical chemists.

To the medical practitioner twenty years out of medical school, this book will seem not only mystical but probably also unintelligible. Nevertheless, present-day premedical education is such that the author is justified in stating that the "text of this book can be readily understood by the average medical student." The more complicated mathematics is relegated to an appendix. Reference footnotes and diagrams abound in simple but instructive form. Adequate indexes of subjects and authors are appended.

This short volume should appeal to all who take pleasure in the understanding of vital mechanism.

**Some Factors in the Localisation of Disease in the Body.** By Harold Burrows, C.B.E., F.R.C.S., Assistant at the Research Institute of the Cancer Hospital (Free), Consulting Surgeon to the War Memorial Hospital, Gosport; Late Consulting Surgeon, His Majesty's Forces; Late Hunterian Professor, Royal College of Surgeons. Cloth. Price, \$4.50. Pp. 299, with 8 colored plates. New York: William Wood & Company, 1932.

This is a unique work that wanders in a highly speculative field and at the same time makes practical use of its material. The title is a bit misleading. One would suspect that the book dealt with the reasons why diseases selected certain portions of the body for their point of attack. This is true, but the author also discusses the limitation of disease processes, *secundum artem*, using the knowledge gained in studying the various biologic and physiologic tissue changes both in experimental animals and in patients. The study of these changes takes the author into the fields of biology, physics, chemistry and electricity. With much of this work as a basis, new conceptions must be built up concerning certain ill-understood diseases. The author mentions in this connection epilepsy, puerperal sepsis and chronic arthritis.

The book deals first with the localization of foreign proteins, dyes, pigments, syphilis, bacteria, virus and cancer. It then deals with the factors that promote and limit specific localization in the tissues. The final division discusses the practical application of the facts gleaned from the study of localization and its attendant factors.

As stated, the book is highly speculative, and there are many statements that cannot at present be well supported. The whole work, however, has a convincing atmosphere that must serve as a stimulus for further investigation along similar lines.

**Tactique opératoire du pancréas et de la rate.** By J. Okinczyc and L. Auroiseau. Price, 75 francs. Pp. 267. Paris: Gaston Doin & Cie, 1933.

A great deal of interesting material is compressed into this volume, and while a description of surgical technic is the primary purpose, one learns about the general problems of pancreatic and splenic disease as well. Of especial value is the analysis of surgical experience in the past which has led up to present methods. The book is well illustrated and indexed, and the bibliography is especially rich in French titles. The book should prove of great value to the American reader who wishes to familiarize himself with French practice in connection with the surgery of the spleen and the pancreas.



## THERAPEUTIC EFFECT OF TOTAL ABLATION OF NORMAL THYROID ON CONGESTIVE HEART FAILURE AND ANGINA PECTORIS

### III. EARLY RESULTS IN VARIOUS TYPES OF CARDIOVASCULAR DISEASE AND COINCIDENT PATHOLOGIC STATES WITHOUT CLINICAL OR PATHOLOGIC EVIDENCE OF THYROID TOXICITY

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This communication is a report on the therapeutic results of total ablation of the normal thyroid gland in a series of 10 patients with congestive heart failure or angina pectoris. Patient G. F. (case 11), on whom this procedure was first performed, was the subject of a previous report;<sup>1</sup> included here is an account of his subsequent clinical course.

The clinical observations which provided the rationale for this procedure began in 1924 with the development of an accurate method for measuring the velocity of the blood flow through the lungs.<sup>2</sup> Measure-

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This study was aided by a grant from the William W. Wellington Memorial Research Fund of Harvard University.

From the Medical and Surgical Services and the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard University Medical School.

1. Blumgart, H. L.; Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch. Int. Med.* **51**:866 (June) 1933.

2. (a) Blumgart, H. L., and Yens, O. C.: The Rate of Blood Flow as Determined by a New Method, *Am. J. Physiol.* **72**:1, 1925; (b) Studies on the Velocity of Blood Flow: I. The Method Utilized, *J. Clin. Investigation* **4**:1, 1927. (c) Blumgart, H. L., and Weiss, S.: The Velocity of Venous Blood to the Right Heart in Man, *Proc. Soc. Exper. Biol. & Med.* **23**:694, 1926; (d) Studies on the Velocity of Blood Flow: II. The Velocity of Blood Flow in Normal Resting Individuals, and a Critique of the Method Used, *J. Clin. Investigation* **4**:15, 1927;

*(Footnote continued on page 166)*

ments in more than 600 subjects demonstrated that, normally, the velocity of flow was directly determined by the metabolic demands of the body.<sup>3</sup> The metabolic demands of the body were gaged by the basal metabolic rate. When the metabolic rate was accelerated, as in thyrotoxicosis,<sup>3a</sup> the speed of blood flow was proportionately increased; on the other hand, when the metabolic rate was depressed, as in myxedema,<sup>4</sup> the blood velocity was correspondingly lowered. Patients with compensated heart disease were found to have a blood velocity within normal limits, in accord with the normal level of the basal metabolic rate. But in subjects with congestive heart failure, in spite of a normal metabolic rate, the blood velocity was considerably slowed. This lack of correspondence offered an explanation for the presence of the symptoms and signs of decompensation which were in proportion to the degree of slowing of the blood velocity.<sup>5</sup> The corollary of these observations was obvious: Since therapeutic attack directed toward the

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(e) VI. The Method of Collecting the Active Deposit of Radium and Its Preparation for Intravenous Injection, *ibid.* 4:389, 1927; (f) VII. The Pulmonary Circulation Time in Normal Resting Individuals, *ibid.* 4:399, 1927; (g) IX. The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardiovascular Disease, *ibid.* 5:343, 1928.

3. (a) Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: III. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Rheumatic and Syphilitic Heart Disease, *J. Clin. Investigation* 4:149, 1927; (b) IV. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Arteriosclerosis and in Patients with Arterial Hypertension, *ibid.* 4:173, 1927; (c) footnote 2f; (d) Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: XIII. The Circulatory Response to Thyrotoxicosis, *J. Clin. Investigation* 9:69, 1930.

4. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: XIV. The Circulation in Myxedema with a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis, *J. Clin. Investigation* 9:91, 1930.

5. (a) Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: V. The Physiological and the Pathological Significance of the Velocity of Blood Flow, *J. Clin. Investigation* 4:199, 1927; (b) X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, *ibid.* 5:379, 1928; (c) XI. The Pulmonary Circulation Time, the Minute Volume Blood Flow Through the Lungs, and the Quantity of Blood in the Lungs, *ibid.* 6:103, 1928; (d) Weiss, S., and Blumgart, H. L.: The Effect of the Digitalis Bodies on the Velocity of Blood Flow Through the Lungs and on Other Aspects of the Circulation: A Study of Normal Subjects and Patients with Cardiovascular Disease, *ibid.* 7:11, 1929; (e) Studies on the Velocity of Blood Flow: VII. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Pulmonary Emphysema, *ibid.* 4:555, 1927.

circulation in chronic heart failure is unavailing, the way to relieve the circulation is to decrease the load on it by lowering the basal metabolic rate, i. e., by thyroidectomy. Subtotal thyroidectomy produced only temporary improvement.<sup>1</sup> It was not long before it was realized that anything short of complete removal of every vestige of thyroid gland would not permanently lower the metabolic rate, and that to accomplish this it was necessary to perform total ablation of the thyroid. Equilibrium between the metabolic rate and the blood velocity thus effected was found to restore compensation.<sup>1</sup>

#### HISTORICAL RÉSUMÉ

*Relation Between Metabolic Rate and Velocity of Blood Flow.*—An adequate flow of blood to the tissues implies two things. In the first place, an adequate amount of blood must be expelled from the heart per unit of time. In the second place, this blood must be transported to the sites of utilization at an adequate speed. Because measurements of the cardiac output are technically difficult and are not applicable to patients with congestive failure, studies of the velocity of blood flow were undertaken.<sup>6</sup> Measurements of any such single aspect of the circulation give an inevitably incomplete picture of all the circulatory changes within the body. They afford, however, insight into the general pathologic physiology of the circulation. When this information is correlated with the clinical findings and measurements of other important characteristics of the circulation, a clearer understanding of the nature of circulatory insufficiency is made possible.<sup>6</sup>

After a study of the velocity of blood flow in patients with normal basal metabolic rates, the circulation in thyrotoxicosis was studied, for this condition seemed to offer an exceptional opportunity to observe the effects of an increased metabolic rate on the circulation uncomplicated by many extraneous factors. In such patients without clinical evidence of cardiovascular disease, the velocity of blood flow was strikingly increased.<sup>3d</sup> This finding was in accord with the results of Bock<sup>7</sup> and of others,<sup>8</sup> which indicated that the minute volume output of the heart

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6. Blumgart, H. L.: *The Velocity of Blood Flow in Health and Disease: The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation*, Medicine **10**:1, 1931.

7. Bock, A. V., quoted by Means, J. H.: *Circulatory Disturbances in Diseases of the Glands of Internal Secretion*, Endocrinology **9**:192, 1925.

8. (a) Burwell, C. S.; Smith, W. C., and Neighbors, D. W.: *The Output of the Heart in Thyrotoxicosis with a Report of a Case of Thyrotoxicosis Combined with Primary Pernicious Anemia*, Am. J. M. Sc. **178**:157, 1929; (b) Liljestrand, G., and Stenström, N.: *Clinical Studies on the Work of the Heart During Rest: I. Blood Flow and Blood Pressure in Exophthalmic Goiter*, Acta med. Scandinav. **63**:99, 1925; (c) Means, J. H., and Newburgh, L. H.: *Studies of the Blood Flow by the Method of Krogh and Lindhard*, Tr. A. Am. Physicians **30**: 51, 1915.

in thyrotoxic patients at rest corresponded to that in normal persons doing light work. These findings indicated the strain under which the heart labored in persons with elevated metabolism, even when at rest, and explained the frequency of circulatory insufficiency in thyrotoxicosis. The extent of the increase in the velocity of blood flow through the lungs was closely related to the extent of increase in the basal metabolic rate. This relationship was present in every instance and indicated the degree to which the velocity of blood flow was necessarily increased to support the metabolic needs of the tissues.

Several patients with essential hypertension but without clinical evidence of thyrotoxicosis were also studied.<sup>3d</sup> In some of these patients the basal metabolic rate was elevated as high as plus 33 per cent. The increase in the velocity of blood flow through the lungs was similar to that observed in thyrotoxic patients with equally high metabolic rates but without hypertension. These findings were in accord with certain observations on the minute volume output of the heart.<sup>9</sup> It was felt that the increased velocity of blood flow through the lungs in these conditions was due to the elevated metabolism rather than to a specific toxic effect on the heart.<sup>3d</sup>

In patients with congestive failure, the speed of blood flow was slower than in comparable compensated persons with the same basal metabolic rate.<sup>2g</sup> Thyrotoxic patients with clinical evidence of cardiovascular disease were studied.<sup>3d</sup> These patients complained of dyspnea on the slightest exertion. In them, the velocity of blood flow, though faster than normal, was not so fast as that of patients with similarly elevated basal metabolic rates who showed no evidence of cardiovascular disease.

Patients with circulatory insufficiency and presumably a normal basal metabolic rate also showed a decided slowing in blood flow, even when early symptoms of circulatory insufficiency, such as palpitation on exertion, had occurred. With the appearance of more advanced signs of congestive failure, the retardation in the speed of blood became more pronounced and generally paralleled the degree of circulatory failure. It became apparent that circulatory insufficiency consists in the failure of the heart to maintain a blood supply adequate to the ordinary needs of the tissues at any given metabolic level.<sup>6</sup>

Of particular interest were the findings in patients with myxedema. In these patients a degree of slowing in the blood flow through the lungs was found, which corresponded closely with the degree to which the

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9. Blalock, A., and Harrison, T. R.: The Effects of Thyroidectomy and Thyroid Feeding on the Cardiac Output, *Surg., Gynec. & Obst.* **44**:617, 1927. Davies, H. W.; Meakins, J., and Sands, J.: Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood: V. The Blood Gases and Circulation Rate in Hyperthyroidism, *Heart* **11**:299, 1924. Liljestrand and Stenström.<sup>8b</sup>

metabolic rate was lowered. The slowing of the blood flow in myxedema was not entirely unexpected, but the degree of slowing was striking, being almost as great as that observed in patients with rheumatic valvular heart disease and auricular fibrillation, who had previously suffered from severe circulatory decompensation and showed symptoms or signs of congestive failure at the time of the test.<sup>4</sup> None of the myxedematous patients, however, showed evidence of cardiovascular disease. The fact that the myxedematous patients showed no evidence of circulatory insufficiency with a speed of blood flow approximately the same as that of decompensated persons demonstrated the fact that the adequacy of a given speed of blood flow can be decided only in relation to the metabolic needs of the tissues.<sup>4</sup>

The thought therefore arose that if the normal metabolic rate of the patient with congestive failure were reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of his body. In terms of the law of supply and demand, the supply of blood in such a patient with congestive failure would not be increased, but the metabolic demands of his body would be decreased to a level in conformity with his blood supply.

These considerations in regard to congestive failure were equally applicable to angina pectoris.<sup>10</sup> The higher the metabolic rate, the greater are the output of the heart and the velocity of blood flow. The consequent increased work of the heart necessitates an increased coronary blood supply. Because of these considerations and because the intrinsic metabolic needs of the myocardium rise along with those of the rest of the body, the blood supply to the heart must be greater at normal metabolic rates than at the lower rate of myxedema. With arteriosclerotic narrowing of the coronary vessels, the blood supply of the heart through these vessels may be inadequate to the needs of a normal metabolic rate although sufficient for the needs of the heart at lower metabolic rates.

This analysis of the relation of the clinical manifestations of circulatory insufficiency to the metabolic needs of the tissues and the concept that a permanently lowered metabolism may be beneficial to patients with congestive failure or angina pectoris of nonthyrogenous origin were in accord with available knowledge in the literature.

*Relation Between Thyrotoxicosis and Heart Disease.*—Beginning with the earliest descriptions of thyrotoxicosis, numerous observers have

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10. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: XV. The Velocity of Blood Flow and Other Aspects of the Circulation in Patients with "Primary" and Secondary Anemia and in Two Patients with Polycythemia Vera, *J. Clin. Investigation* 9:679, 1931. Starling, E. H.: *The Linacre Lecture on the Law of the Heart*, New York, Longmans, Green & Co., 1918.

noted the frequent occurrence of congestive failure or of angina pectoris in this disease and improvement in the circulation with subsidence of thyroid activity. Parry's original account of exophthalmic goiter in 1825 appears at the beginning of the chapter entitled "Diseases of the Heart."<sup>11</sup> *"Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the heart. Case 1.* There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed, in that connection, by medical writers. The malady to which I allude is enlargement of the thyroid gland." In some patients, Parry noted the appearance of congestive failure or of angina pectoris with the development of the classic signs of exophthalmic goiter; in others, angina pectoris or palpitation and nervousness appeared several months before enlargement of the thyroid. Parry also clearly recorded subsidence of congestive failure with a decrease in the enlargement of the thyroid gland.

After the original accounts of the disease, practically all the signs and symptoms of the condition that are now known, according to Means,<sup>12</sup> were recognized and described by such masters as Trousseau,<sup>13</sup> Marie<sup>14</sup> and Charcot.<sup>15</sup> With the advent of operative treatment made possible by the work of Billroth<sup>16</sup> and the classic contributions of Kocher,<sup>17</sup> the effect of thyroidectomy on congestive failure was again clearly stated. In the extensive report of Kocher's cases by his son in 1902, the disappearance of congestive failure following thyroidectomy is described.<sup>18</sup> In the latter part of the nineteenth and the earlier years of the twentieth century, clinical interest was reawakened in various

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11. Parry, C. H.: Collections from Unpublished Medical Writings, London, Underwoods, 1825, vol. 2.

12. Means, J. H., and Richardson, E. P.: The Diagnosis and Treatment of Diseases of the Thyroid, in Christian, H. A.: Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4.

13. Trousseau, A.: Lectures on Clinical Medicine, translated by P. V. Bazire, Philadelphia, Lindsay & Blakiston, 1867, vol. 1, p. 542.

14. Marie, P.: Sur la nature et sur quelques-uns des symptômes de la maladie de Basedow, Arch. de neurol. **6**:79, 1883.

15. Charcot, J. M.: Maladie de Basedow (goître exophthalmique); formes frustes; nouveau signe physique; traitement par l'électricité, Gaz. d. hôp. **58**:98 and 113, 1885.

16. Billroth, T.: Chirurgische Klinik, Zürich, 1860-1867, Berlin, A. Hirschwald, 1869. Wölfler, A.: Die Kropfextirpationen an Billroth's Klinik von 1877 bis 1881, Wien. med. Wchnschr. **32**:5, 1882.

17. Kocher, T.: Zur Pathologie und Therapie des Kropfes, Deutsche Ztschr. f. Chir. **10**:191, 1878; Ueber Kropfextirpation und ihre Folgen, Arch. f. klin. Chir. **29**:254, 1883.

18. Kocher, A.: Ueber Morbus Basedowi, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **1**:1, 1902.

types of thyrotoxicosis in which several or many of the characteristic features are absent, increasing reliance being placed on measurements of the basal metabolic rate and, since 1923, on the response to iodine therapy before operation.<sup>19</sup> Of particular interest were the careful studies of Hamilton,<sup>20</sup> begun in 1920, on the effect of subtotal thyroidectomy in 50 patients with signs of congestive heart failure due to hyperthyroidism. He concluded that "The response to treatment . . . is indeed unique." In 1931, Morris maintained that the basal metabolic rate in patients with thyrotoxicosis could be within normal limits. He described a group of cases of "'thyroid heart' with low basal metabolic rate" in which, he stated, "the basal metabolic rate has been normal or subnormal; yet their response to subtotal thyroidectomy has differed in no way from that of patients with similar symptoms and increased metabolic rate." Morris concluded that "when evidence of a pre-existing thyrotoxic state is found, even with a subnormal basal metabolic rate, subtotal thyroidectomy may be indicated."<sup>21</sup> Recently Rosenblum and Levine reported the results of subtotal thyroidectomy in a group of patients with hyperthyroidism and significant heart disease.<sup>22</sup> They found immediate marked improvement which was extremely well maintained. One of this series of patients with hyperthyroidism and significant heart disease improved after the administration of compound solution of iodine. The removed portion of the gland appeared normal, leading the authors to infer that "the metabolism test, even when within normal limits, may not absolutely rule out active hyperthyroidism, or the finding of a normal gland may not mean that the gland has been

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19. Minnich, W.: *Das Kropfherz und die Beziehungen der Schilddrüsenerkrankungen zu dem Kreislaufapparat*, Vienna, Franz Deuticke, 1904. Mobius, P. J.: *Die Basedowische Krankheit*, in Nothnagel: *Encyclopedia of Practical Medicine*, Philadelphia, 1896, vol. 22, p. 1. Romberg, Ernst: *Lehrbuch der Krankheiten des Herzens und der Blutgefäße*, Stuttgart, Ferdinand Enke, 1921. Dameshek, W.: *The Heart in Hyperthyroidism*, Boston M. & S. J. **190**:487, 1924. Lahey, F. H., and Hamilton, B. E.: *Thyrocardiacs: Their Diagnostic Difficulties; Their Surgical Treatment*, Surg., Gynec. & Obst. **39**:10, 1924. Kerr, W. J., and Hensel, G. C.: *Observations of the Cardiovascular System in Thyroid Disease*, Arch. Int. Med. **31**:398 (March) 1923. Plummer, H. S.: *Results of Administering Iodin to Patients Having Exophthalmic Goiter*, J. A. M. A. **80**: 1955 (June 30) 1923.

20. Hamilton, B. E.: *Clinical Notes on Hearts in Hyperthyroidism*, Boston M. & S. J. **186**:216, 1922; *Heart Failure of the Congestive Type Caused by Hyperthyroidism*, J. A. M. A. **83**:405 (Aug. 9) 1924.

21. Morris, R. S.: *The "Thyroid Heart" with Low Basal Metabolic Rate*, Am. J. M. Sc. **121**:297, 1931; *Thyrotoxic Circulatory Symptoms with Low Metabolic Rate*, Am. Heart J. **6**:730, 1931.

22. Rosenblum, H. H., and Levine, S. A.: *What Happens Eventually to Patients with Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy?* Am. J. M. Sc. **185**:219, 1933.

functioning normal. Finally, it is possible that partial removal of a normal gland may be helpful in patients who have either angina pectoris or the congestive type of heart failure." Several investigators have performed subtotal thyroidectomy on patients with no clinical thyrotoxicosis without producing clinical improvement or permanently lowering the metabolic rate. Rose,<sup>22a</sup> in 1932, discussed the difficulties in differential diagnosis between malignant hypertensive vascular disease and hyperthyroidism, even after prolonged observation of the patient. He noted that Riesman,<sup>22b</sup> in 1919, and Boas and Shapiro,<sup>22c</sup> in 1925 and 1926, had described hypertensive patients with loss of weight, tachycardia, diastolic hypertension, persistently elevated basal metabolism, nervousness and pigmentation of the skin but without definite thyrotoxicosis. Subtotal thyroidectomy in 3 of the cases was without effect. Rose reported a similar case in which "maximal subtotal thyroidectomy" was performed, a small amount of thyroid tissue being left at the upper pole of each lateral lobe. The gland appeared normal grossly and microscopically. The elevated basal metabolic rate and clinical course were unaffected, the patient dying in coma five months later. Rose concluded that "the result in this case certainly does not support our thought that thyroidectomy might favorably influence the course of malignant hypertension. However, we were not successful in producing any manifestations of hypothyroidism despite the amount of thyroid tissue removed. The persistent elevation of the basal metabolism and absence of thyreoprival symptoms after operation is noteworthy. It is conceivable that if a sufficient degree of hypothyroidism could be thus produced, cardiac overactivity might be reduced, the pulse rate decreased, and the arterial tension possibly lowered." Partial suprarenalectomy and subtotal thyroidectomy were performed on 2 patients with cardiovascular disease and 1 patient with arterial hypertension by Crile<sup>23</sup> without encouraging results. These patients were evidently in a state of "pathologic emotional or nervous excitation," but were not thyrotoxic. Crile hoped by such operations to minimize the "excessive uncontrolled activity or kinetic drive." These failures to observe improvement which would justify application of the procedure to other patients is understandable in the light of our own failures

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22a. Rose, E.: Malignant Hypertensive Vascular Disease Simulating Hyperthyroidism: Clinical Course Following Maximal Subtotal Thyroidectomy, *M. Clin. North America* **16**:261, 1932.

22b. Riesman, D.: Hypertension in Women, *J. A. M. A.* **73**:330 (Aug. 2) 1919.

22c. Boas, E. P., and Shapiro, S.: Diastolic Hypertension with Increased Basal Metabolic Rate, *J. A. M. A.* **84**:1558 (May 23) 1925; Further Observations on Patients with Hypertension and Increased Basal Metabolic Rate, *Am. Heart J.* **1**: 643 (June) 1926.

23. Crile, G.: The Treatment of Certain Types of Hyperthyroidism, *Tr. Am. A. Study Goiter* **1**:1, 1932.



when subtotal thyroidectomy was performed, and illustrates the necessity of complete ablation of the thyroid gland.

*The Effect of the Administration of Thyroid Substance to Patients with Myxedema.*—The administration of thyroid substance to patients with myxedema is followed by a rise in the basal metabolic rate and a proportionate increase in the speed of blood flow.<sup>4</sup> This increased speed of blood flow denotes an increased amount of work on the part of the heart and serves to explain the observations showing that the administration of thyroid to such patients may precipitate angina pectoris or circulatory failure. These considerations were likewise in accord with the ideas underlying the proposed investigation.

#### PLAN OF INVESTIGATION AND METHODS

The course of chronic heart disease is often irregular and characterized by periods of unexpected exacerbation and remission. The fact that recovery from such remissions may be complete for varying periods made it imperative to select only patients in whom the course of the disease had been progressive and who showed evidence of incapacity even during a period of remission. The patients with congestive failure had all been treated by rest in bed for a long period, and although they may have been free from symptoms after prolonged rest in bed they regularly showed evidence of congestive failure on getting out of bed. The condition in each case was such that definite improvement could be confidently attributed to the operative procedure.

It was difficult to obtain patients who met with these requirements, for many who presented a history of progressive disease failed to give sufficient objective confirmation of their incapacity when carefully studied by exercise and other tests. For this reason, the situation in each case was appraised independently by several observers before a decision was reached. Patients with a history of angina pectoris were studied under standard conditions after exercise, and it was shown that a number of them did not have true angina pectoris.

It was imperative to select patients who were fair operative risks. Obviously, a patient was not a good risk at the height of an acute exacerbation with signs and symptoms of congestive failure. It was therefore necessary in some cases to wait for a period of improvement and to exert every effort to relieve such signs as edema, for example, by diuretics.

No patient was chosen whose prognosis for life was good. In each instance the operation was offered to the patient with a full account of its experimental status without minimizing the risk of operation. No better gage of the predicament of most of these patients could be found than their pathetic desire to hazard any of the dangers involved in order

to secure possible benefit after having suffered for many years and after having observed their condition become progressively worse in spite of medical treatment.

The patients selected had diverse types of cardiovascular disease, i. e., arteriosclerotic heart disease with congestive failure, arteriosclerotic heart disease with angina pectoris, arteriosclerotic heart disease with hypertension and paroxysmal dyspnea, cor pulmonale with right ventricular failure, and rheumatic valvular heart disease with normal rhythm or with auricular fibrillation. One of the patients, aged 66, had aortic insufficiency, and the serologic tests for syphilis were positive. He had suffered from dyspnea for many years, and it was felt that the primary cause of his symptoms and signs was cardiovascular arteriosclerosis.

Patients with circulatory failure due to syphilitic cardiovascular disease were not chosen for this study because of the rapid progression once the signs and symptoms of circulatory insufficiency appear.<sup>24</sup> Patients with active rheumatic infection, recent vascular accidents or the active phases of acute coronary thrombosis, and those unable to describe their symptoms clearly and accurately were not chosen. No symptoms or signs of thyrotoxicosis were present; no patient gave a history of preexisting thyrotoxicosis. Physical examination of the thyroid gave normal findings. Pathologically, the glands were normal, except in patient W. L. (case 7), whose thyroid showed quiescent colloid nodular goiter. We have not operated on patients who have not reached physical maturity. It may be possible, however, to obviate the danger of possible cretinism in such cases by administering small amounts of thyroid substances and at the same time to relieve some of the burden on the heart.

Detailed clinical study of the preoperative and postoperative condition of each patient was carried out independently by several observers. The patients were studied before operation for periods ranging from two weeks to several months. This was done not only to appraise the clinical condition as accurately as possible but also to improve the condition and so minimize the risk of operation. As we realize the inevitable importance of suggestion in any therapeutic procedure, we have attempted to evaluate the preoperative and postoperative condition of our patients by as many objective criteria as possible. Daily measurements of the blood pressure, the vital capacity of the lungs and the body weight were made under standardized conditions. Roentgenograms of the chest taken at a distance of 7 feet (213 cm.) were made several days before operation and were repeated once a month, or more

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24. Scott, R. W.: Symptoms and Clinical Course of Syphilitic Aortic Insufficiency, *Am. Heart J.* **6**:86, 1930. White, P. D.: *Heart Disease*, New York, The Macmillan Company, 1931.

often if indicated. Electrocardiographic tracings in most cases were obtained at ten day intervals. Photographs were also taken before and after operation.

The basal metabolic rate was measured with a Collins Benedict-Roth apparatus. Sedatives were not given the night preceding the determination of the basal metabolism. Patients with orthopnea were allowed to lie in a semirecumbent position. On each occasion measurements were made in duplicate or triplicate. Measurements were repeated frequently before operation until it was evident that the patient was under truly basal conditions and until successive tests on different days agreed within 5 per cent. The basal metabolic rate was again estimated after operation, as soon as the patient's condition allowed, and was repeated at approximately weekly intervals. The Aub-Du Bois normal standards were used.<sup>25</sup>

The venous pressure was measured by the direct venipuncture method of Moritz and Tabora.<sup>26</sup> When possible, the readings were obtained with the patient recumbent, the right auricle being assumed to be 5 cm. below the level of the fourth costochondral junction. When orthopneic, the patient was allowed to sit up at an angle of 45 degrees, the right auricle then being assumed to be 2.5 cm. below the fourth costochondral junction. The accuracy of these assumptions has been checked by measurements of the venous pressure in the same patient in both positions.

The arm to tongue circulation time was used as an index of the velocity of blood flow, according to the method of Winternitz, Deutsch and Brüll.<sup>27</sup> From 3 to 5 cc. of sodium dehydrocholate (decholin) was injected into an antecubital vein, and the time of arrival in the tongue was estimated by a signal from the patient when he experienced a bitter taste in the mouth.<sup>27a</sup> The results by this method were found to conform satisfactorily with measurements of the "arm to arm circulation time" and "crude pulmonary circulation time" of previous studies by the radioactive method. A number 18 or 16 gage needle was used in order to shorten the time of injection and to facilitate a sharp end-point of detection in the presence of marked slowing in the blood flow. Measurements of the velocity of blood flow were made in triplicate at the same

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25. Aub, J. C., and Du Bois, E. F.: Clinical Calorimetry: XIX. The Basal Metabolism of Old Men, *Arch. Int. Med.* **19**:823 (May, pt. 2) 1917.

26. Moritz, F., and Tabora, D. V.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu Bestimmen, *Deutsches Arch. f. klin. Med.* **98**:475, 1910.

27. Winternitz, M.; Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlauzeit mittels Decholininjektion, *Med. Klin.* **27**:986, 1931.

27a. The ampules of decholin were supplied by Mr. Paul de Haen of Riedel-de Haen, Inc.

venipuncture and were accepted only when at least two determinations checked within two seconds. The circulation time was usually estimated in conjunction with the measurements of the venous pressure. Before operation the tests were carried out and checked on at least two different days. After operation the circulation time and the venous pressure were determined at approximately weekly intervals. The average normal arm to tongue circulation time by the decholin method is eighteen seconds.<sup>28</sup>

In addition to the usual laboratory examination of the blood, the level of various substances in the blood serum during fasting was measured before and at varying intervals after operation. The substances measured included nonprotein nitrogen, sugar, inorganic phosphate, calcium, cholesterol, total protein, albumin, globulin, carbon dioxide content and the icteric index. The blood was obtained from an antecubital vein with minimum stasis, and was collected and centrifuged under oil.

The simple exercise tolerance tests for patients with congestive failure were found not entirely satisfactory because of the degree of disability shown by our subjects. Master and Oppenheimer<sup>29</sup> gaged the degree of cardiac disability by determining the maximum amount of work which patients could perform in one and one-half minutes and still have the pulse and blood pressure return to the resting level within two minutes after the completion of the exercise. The work consisted in repeatedly climbing a staircase of 2 steps, each being 9 inches (22.9 cm.) high. They presented, for comparison, tables indicating the amount of work which normal persons could perform under similar conditions. This test offers the advantage of simplicity and freedom from the necessity of training. Its disadvantage lies in the ease of fatigability of cardiac patients, making it impossible to repeat the test at frequent intervals.

In the test as performed by us the patient remained seated until the pulse and blood pressure became stationary. He then performed the amount of work specified in the tables of Master and Oppenheimer for normal persons of the same age, weight, sex and height. An attempt was made to have the patient perform the necessary number of trips within one and a half minutes, following which he immediately returned to his chair. The pulse rate and blood pressure were recorded at intervals of one-half minute until they returned to their original resting level.

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28. Gargill, S. L.: The Use of Decholin as a Clinical Test of the Velocity of Blood Flow, *New England J. Med.*, to be published.

29. Master, A. M., and Oppenheimer, E. T.: A Simple Exercise Tolerance Test for Circulatory Efficiency with Standard Tables for Normal Individuals, *Am. J. M. Sc.* **177**:223, 1929.

The following observations were made: (1) the degree of facility displayed by the patient and the length of time necessary to perform the amount of work prescribed; (2) the degree of fatigue produced; (3) the pulse rate during rest and the pulse curve following exercise; (4) the blood pressure level at rest and the blood pressure curve following exercise; (5) the degree and duration of dyspnea, cyanosis and other signs of circulatory embarrassment following work.

The exercise tolerance test was performed on two separate days before operation, a few days after the patient had been allowed to walk for the first time after operation and subsequently at approximately weekly intervals throughout the patient's stay in the hospital. In a patient with angina pectoris, the condition was evaluated objectively by measuring the type and amount of exercise necessary to precipitate an attack under accurately controlled conditions. A more detailed description of this test will be found in the history of the case.

#### REPORT OF CASES

CASE 1.—*Rheumatic heart disease, mitral stenosis and insufficiency, dyspnea and hemoptysis for seven years; attacks of congestive failure for five years.*

E. W., a man, aged 27, an unskilled worker, was transferred to the Beth Israel Hospital on March 8, 1933, through the kindness of Dr. Roger D. Mackey, Lieutenant Commander, Medical Corps, United States Navy. He complained of progressive shortness of breath and repeated hemoptysis of seven years' duration. He had rheumatic fever at the age of 6, with yearly recurrences for four years and a final attack in 1926 at the age of 20. The present illness began in 1926, seven years before admission, when he noticed that he tired easily and frequently coughed up small amounts of blood. During the next two years these symptoms increased, hemoptysis amounting to one or two wine glasses full and occurring every three or four weeks. He was finally forced to bed in 1928 for two and a half weeks. After this he returned to work, in spite of dyspnea, orthopnea and marked palpitation. Hemoptysis increased to approximately one-half cupful and occurred two or three times a week. In 1930 he was forced to leave his job although he was working but very little. Orthopnea and dyspnea became marked. Attacks of sharp intermittent pains appeared substernally, posteriorly between the shoulder blades and in both axillae. The pains lasted from two to three hours, were usually precipitated by movement, particularly after getting into bed, and were relieved somewhat by rest.

During the next two years, from 1930 to 1932, the patient spent several weeks in bed at home and in several hospitals. In 1932 he entered a hospital in Maine with generalized anasarca. He remained there for seven months, hemoptysis occurring almost daily, interrupted by occasional periods of freedom from this symptom, the longest period being two weeks. In February, 1933, he was admitted to a hospital near Boston, apparently moribund and suffering from congestive failure with general anasarca, hemoptysis and intense respiratory distress. After five weeks of complete rest in bed he was transferred to the Beth Israel Hospital.

Physical examination shortly after he came under our supervision revealed a well developed, alert young man, propped up in bed, moderately dyspneic, with slight cyanosis of the lips and malar prominences. The apex impulse was diffuse in the sixth interspace, 12.5 cm. to the left of the midsternal line. The cardiac

rhythm was regular; the rate was 100 per minute. The first sound at the apex and the second pulmonic sound were accentuated. At the mitral area there were a systolic blow and a diastolic rumbling murmur. The blood pressure was 110 systolic and 60 diastolic. At the base of the left lung there were dulness, diminished vocal fremitus and medium crepitant râles. The lungs were otherwise clear. In the right upper quadrant of the abdomen there were increased resistance and tenderness, although a definite edge of the liver was not felt. The fingers showed slight clubbing.

Studies of the urine and blood gave normal findings. A roentgenogram of the chest taken at a distance of 7 feet showed the transverse diameter of the heart to be 17.3 cm., and the internal diameter of the chest, 31.8 cm.; there was marked prominence in the region of the auricles. The pulmonary markings were considerably increased, and the bases of both lungs showed diminished radiance consistent with pulmonic fibrosis of cardiac origin. Electrocardiographic tracings showed normal sinus rhythm, a P R interval of 0.22 seconds and right axis deviation. Repeated measurements showed variations in venous pressure from 4.4 to 12.3 cm. of water. The velocity of blood flow by the decholin method ranged from twenty-one to twenty-four seconds. The basal metabolic rates, determined on two successive occasions, were plus 4 and plus 7 per cent, respectively. Exercise tolerance tests were performed to gage the extent of the patient's disability.

On March 17, total ablation of the thyroid gland was performed with the patient under gas-oxygen anesthesia.<sup>30</sup> Pathologic examination showed a normal gland. The patient's condition remained good throughout the operation; the ventricular rate rose from 104 to 135, the blood pressure, to 135 systolic and 70 diastolic; they remained at these levels to the end of the operation, which required one hour and fifty-six minutes. Approximately ten minutes later the patient opened his eyes and was able to talk. The temperature rose to 103 F. after operation and subsided to normal on the fourth day. The respiratory rate, which had shown daily rises to 30 per minute for the nine days preceding operation, rose to 35 immediately after operation, fell to 20 on the third day and continued at this level throughout the patient's stay in the hospital.

On the third postoperative day the patient stated that he felt better than he had just prior to operation. He noticed that he could turn from one side to the other without palpitation. Before operation palpitation occurred with a slight change of position in bed. His breathing was considerably easier, and there was a decrease in the respiratory rate.

The following routine notes were made by the resident physician:

March 28 (eleven days after operation): The patient is breathing decidedly easier, and he is free from palpitation.

April 4: The patient is now up and about, walking around and feeling definitely improved. He states that he breathes more easily and does not feel precordial distress and palpitation.

April 11: The patient continues to show steady and well marked improvement. He is up and about, walking around without any signs of discomfort.

April 14: The patient has gradually increased his activities so that he has been up and about the entire day for the past four days without any period of rest in bed except at night. The lungs show no râles, and the resistance and tenderness in the right upper quadrant have disappeared.

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30. This operation, as well as all others reported in this series, was performed by Dr. David D. Berlin.

Chart 1 shows the changes in the basal metabolic rate and the velocity of blood flow. Striking variations did not occur until the twenty-third day after operation, when the basal metabolic rate fell to minus 19 per cent. The velocity of blood flow, which was slightly prolonged to start with, became markedly prolonged at the time of the fall in the basal metabolic rate. Clinical improvement appeared to antedate slightly the fall in the basal metabolic rate and the prolongation of the circulation time, but the most striking improvement did not occur until later.

The patient stated that for the first time in seven years he was entirely free from the sensation of heaviness and pain in the left anterior part of the chest, a condition he had so long taken for granted that he had hardly commented on it before operation. He could sleep soundly lying perfectly flat in bed and was unaware of his heart action for the first time in five or more years.

A measured amount of exercise before operation resulted in considerable dyspnea and fatigue and a fall in blood pressure accompanied by almost a state

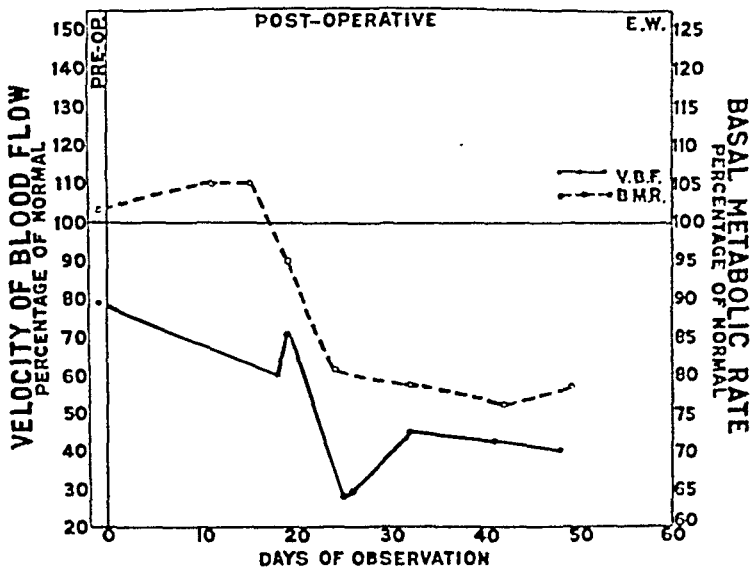


Chart 1 (case 1).—The relation between the velocity of blood flow and the basal metabolic rate.

of collapse. Test performances two weeks after operation showed appreciable improvement. The patient was able to perform the test with greater ease and facility and was less dyspneic and fatigued and the blood pressure rose during the exercise. A test performed seven weeks after operation demonstrated that the patient could do at least 60 per cent more work than was previously possible. Following this exercise the pulse and blood pressure returned to the resting level more rapidly than it had in the less severe preoperative test.

The patient continued to improve and has been up and about, climbing stairs and doing odd jobs, during the last five weeks without dyspnea or palpitation. On two occasions, a few days after thyroidectomy he coughed up small amounts of blood, but except for this he has had no cough or hemoptysis at any time, although before operation this was practically a daily occurrence. The red blood count rose from an average of 4,050,000 to 4,470,000 on the twenty-seventh day after operation, the hemoglobin rising from 55 to 63 per cent (Sahli). The vital capacity, which was relatively high to start with, remained at a level of approximately 3,500 cc. A roentgenogram taken at a distance of 7 feet one month after operation showed no change in the size of the heart. The electrocardiogram

showed an appreciable diminution in the voltage of the Q R S complex and a slight decrease in the height of the T waves.

The only evidence of clinical myxedema consists of a very slight yellowish pallor of the skin, and a slowing in the growth of hair. The patient was quick, responsive, systematic in work and capable of concentrating in a most satisfactory manner.

The patient was discharged on May 6. He left for his residence in New Hampshire and returned on May 23 for a follow-up examination. During the seventeen days of absence he carried on moderate activity, walking without stopping on an average of 1 mile daily. At no time did he show evidence of dyspnea. He slept well, and at no time had there been palpitation or hemoptysis. The vital capacity was 3,500 cc.

*Comment.*—This patient gave a history of repeated attacks of congestive failure since 1928, with cardiac invalidism since July, 1930. After operation conspicuous improvement was shown by the disappearance of palpitation, pain in the chest and hemoptysis. Breathing became easier and orthopnea disappeared, and he was able to perform more physical exercise with less discomfort. Paralleling the clinical improvement the basal metabolic rate became persistently lowered and the velocity of blood flow markedly prolonged. At the time of writing, four months after operation and after three months of moderate activity, the patient showed no evidence of congestive failure. Daily walks of 1 mile or more did not result in dyspnea. Hemoptysis, which was present daily before operation, no longer occurred, and he was restored from a state of physical incapacity to one of occupational usefulness.

*CASE 2.—Rheumatic heart disease, mitral stenosis, aortic insufficiency, extreme cardiac enlargement, auricular fibrillation, pulmonary and renal infarction and attacks of congestive failure for twelve years.*

R. D., a man, 22 years of age, was admitted to the Beth Israel Hospital on March 16, 1933, with a history of shortness of breath of twelve years' duration. He had rheumatic fever at the age of 2, and in 1921, at the age of 10, was admitted to the Children's Hospital in Boston because of active rheumatic heart disease and congestive failure. Two years later he became very short of breath and was admitted to the Massachusetts General Hospital. During the next seven years, from 1922 to 1929, he suffered from shortness of breath, orthopnea, substernal pain, palpitation and edema of the legs, and was admitted four times to the Massachusetts Homeopathic Hospital. At times he was able to be up and do light work, but beginning in 1929 there was a rapid progression of symptoms with frequent attacks of hemoptysis, pain in the anterior part of the chest and palpitation, necessitating almost continuous rest in bed. In June, 1932, he had repeated attacks of massive hemoptysis with dyspnea, cyanosis and prostration, suggestive of pulmonic infarction. During one attack he was sent to the Somerville Hospital, and shortly afterward was transferred to a hospital for chronic diseases. Hemoptysis occurred frequently. In January, 1933, he had an attack of hematuria which persisted for three weeks. During the last six months he had several peculiar fainting spells suggestive of atypical epileptiform seizures. He was practically completely incapacitated, and sat up for only a short period each day.



evident soon after operation, remaining free from pain in the chest and palpitation. There was no orthopnea, and he was out of bed for short periods each day without dyspnea.

Chart 2 shows the changes in the basal metabolic rate and the velocity of blood flow. The metabolism fell rapidly, reaching minus 37 per cent on the fortieth day after operation. The arm to tongue circulation time, which was prolonged before operation, showed further slowing with the marked decrease in the metabolism. At the time when the basal metabolism had fallen to minus 37 per cent, the patient showed some drowsiness which was difficult to evaluate and may have been due to the hypothyroid state. For this reason, thyroid extract was administered. The effect is noted on the chart as a sharp rise in the basal metabolic rate.

Exercise tests showed striking improvement. Before operation, a given amount of exercise resulted in dyspnea, fatigue and a rise in the cardiac rate from 94 to 172 and from 90 to 160 per minute, with pulse deficits of from 70

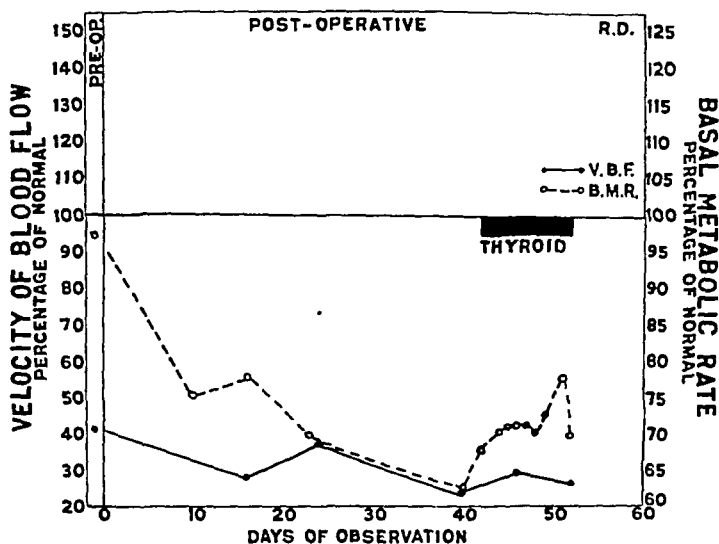


Chart 2 (case 2).—The relation between the velocity of blood flow and the basal metabolic rate.

to 80 per minute. The same performance after operation was carried out with considerably more ease, less dyspnea and no evident fatigue. The rise in the apical rate was from 72 to 148 per minute and from 68 to 80 per minute. Of added interest is the fact that the blood pressure during exercise showed an initial fall before operation in contrast to a definite rise in the performance after thyroidectomy.

Successive electrocardiograms showed a decrease in the voltage of the Q R S complexes from 14 to 8 millivolts. The T waves were not significantly changed. Before operation, the red cell count was 4,640,000; after operation, it rose slightly in spite of an appreciable loss of blood incurred by venesection during the attack of pulmonary edema. The preoperative pulse rate of from 70 to 90 gradually became slowed to 60 and later remained between 50 and 60 during convalescence. The blood pressure remained fairly constant at a level of 120 systolic and 70 diastolic. The vital capacity showed a definite increase immediately after operation to 12 per cent above the preoperative capacity, which ranged from 2,800 to 3,100 cc. Following the attack of pulmonary edema, however, it became diminished but was still somewhat elevated above the preoperative level.

The usual laboratory tests of the urine showed no abnormalities. The Wassermann, Kahn and Hinton tests of the blood were positive for syphilis. A roentgenogram of the heart taken at a distance of 7 feet showed moderate enlargement. There was marked calcification in the walls of the aorta. The electrocardiographic tracing showed normal sinus rhythm, auricular and ventricular premature beats, inverted  $T_1$ , spreading of the QRS complex to 0.12 second and left axis deviation. The venous pressure varied from 3 to 5 cm. of water, and the arm to tongue circulation time, from thirty-two to thirty-six seconds. The metabolic rate was plus 10 per cent repeatedly.

On March 23, 1933, total ablation of a normal thyroid gland was performed with the patient under gas-oxygen anesthesia. The course after operation was smooth and uneventful. The temperature showed no rise. The ventricular rate increased from 60 to 80 beats per minute for three days, and the respirations continued at 20. The pathologist reported the gland to be normal.

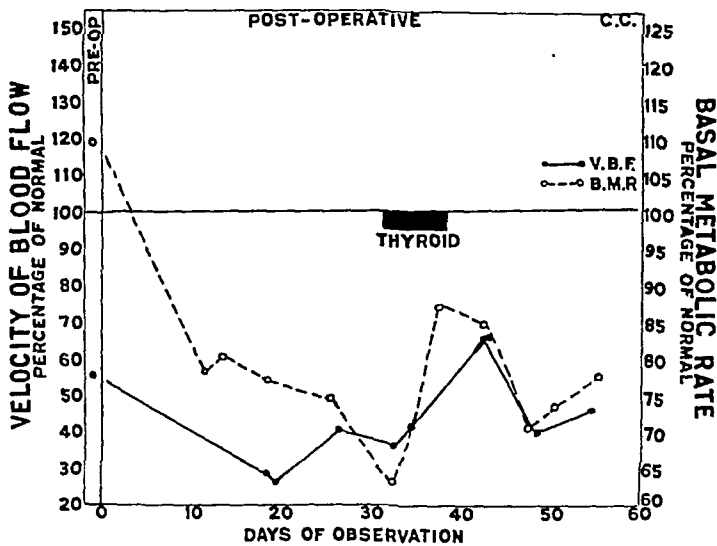


Chart 3 (case 3).—The relation between the velocity of blood flow and the basal metabolic rate.

On the fifth day after operation there was a noticeable change in the patient. He became more cheerful and buoyant and volunteered the information that he felt "ironed out." His palpitation had disappeared, he felt less short of breath, and, for the first time in years, could lie flat without discomfort or difficulty in breathing. Pounding in his chest had been present for so long that he had unconsciously learned to ignore it, and it was only with its disappearance that he realized how continuous it had been and how uncomfortable it had made him.

He was allowed to increase his activity gradually. On the twenty-second day after operation, after having been up and about the ward for about three hours a day during the preceding week, he showed no signs of decompensation. His appetite improved so that the hospital diet had to be increased. In thirty days he gained 10 pounds (4.5 Kg.) without showing any demonstrable edema. The heart rate remained about 60 beats per minute. The vital capacity increased from 600 to 1,200 cc. above the preoperative level. The blood pressure showed very little change, remaining approximately 120 systolic and 70 diastolic. The electrocardiographic tracing no longer revealed premature beats of auricular origin, although ventricular premature beats were still present. There was no significant

later noted the onset of attacks of severe substernal pain, which were relieved within a few minutes by rest. Such attacks occurred about every two weeks. In July, he suddenly became dizzy and was removed to a hospital, where he remained for six weeks. Following discharge he experienced dyspnea and substernal pain on slight exertion, and for the first time he noted swelling of his ankles. On one occasion he was seized with an unusually severe attack of crushing substernal pain which radiated to the inner aspect of his left arm; the pain persisted for several minutes and was accompanied by marked dyspnea and weakness. In September, he was taken to the Boston City Hospital where the diagnosis of cardiac asthma was made. During this admission he had one attack of unconsciousness during which he became pulseless and was not expected to live. Because of his helpless physical condition he was transferred to a hospital for chronic disease. While there he was confined to bed and a wheel chair for several months and was fairly comfortable when so restricted. However, each time he tried to walk or to remain on his feet for even a brief part of the day marked dyspnea and edema of the ankles appeared. From the institution where he had been for sixteen months he was transferred to the Beth Israel Hospital.

Physical examination revealed a poorly nourished, middle-aged man with the general appearance of Paget's disease. The retinal vessels showed evidence of sclerosis. The heart was moderately enlarged, the apex impulse being in the fifth space 12 cm. from the midsternal line. The cardiac action was slow and regular. There was a systolic murmur at the apex. The lungs were clear. The liver was not palpable. The blood pressure was 180 systolic and 90 diastolic. The long bones of the legs, forearms and thighs showed anterior and lateral bowing. There was no edema.

Examination of the urine and blood gave normal findings. A roentgenogram taken at a distance of 7 feet showed the heart enlarged transversely and to the left, the cardiac diameter being 13.6 cm. and the internal diameter of the chest, 24.8 cm. An electrocardiogram showed normal sinus rhythm, the rate being 80. The T waves were inverted in leads II and III. Roentgenograms of the skull and the long bones showed changes typical of Paget's disease. The venous pressure varied from 3 to 6 cm. of water. The arm to tongue circulation time varied from seventeen to twenty-one seconds. The basal metabolic rate varied from plus 7 to plus 12 per cent. The vital capacity of the lungs ranged from 2,100 to 2,700 cc.

On March 24, 1933, total ablation of the normal thyroid gland was performed with the patient under gas-oxygen anesthesia. The operation was uneventful and required one hour and forty minutes. The blood pressure remained at the pre-operative level of 180 systolic and 90 diastolic, the pulse rate not rising above 85. Within a few minutes after the operation the patient was able to talk. The temperature rose to 101 F. on the second day and reached normal on the fifth post-operative day. The pulse showed no elevation above 90.

One week after operation the patient stated that he felt better "all over," that he no longer was conscious of aching and heaviness in the region of his heart, and that he experienced a "lightness" within his chest. He was mentally alert and appeared happy.

The following routine notes were made by the resident physician:

Twenty-one days after operation: The patient ventures that he feels much improved. He appears brighter and is able to walk about with considerably more dexterity than he showed before operation. He states that his voice is hoarse as compared with that before operation.

Twenty-five days after operation: He states that he feels better every day.

Thirty-two days after operation: He insists that he is considerably better than he was before operation. Shaving is now necessary but once in three days, whereas before thyroidectomy it was necessary daily. Examination of the vocal cords by Dr. L. M. Freedman showed paresis of one cord.

Chart 4 shows the change in the basal metabolic rate and the velocity of blood flow after operation. On the fortieth day the metabolic rate had dropped to minus 28 per cent, and the circulation time was correspondingly prolonged. The patient continued to improve, his strength returned, there was no orthopnea, and he was able to be up for short periods during the day without dyspnea. At the time of writing, two months after operation, he had no attacks of angina pectoris or cardiac asthma. He stated that he had not felt as well at any time since before the onset of his illness two years previously. There were no symptoms or signs of congestive failure. An electrocardiogram showed a slight decrease in the

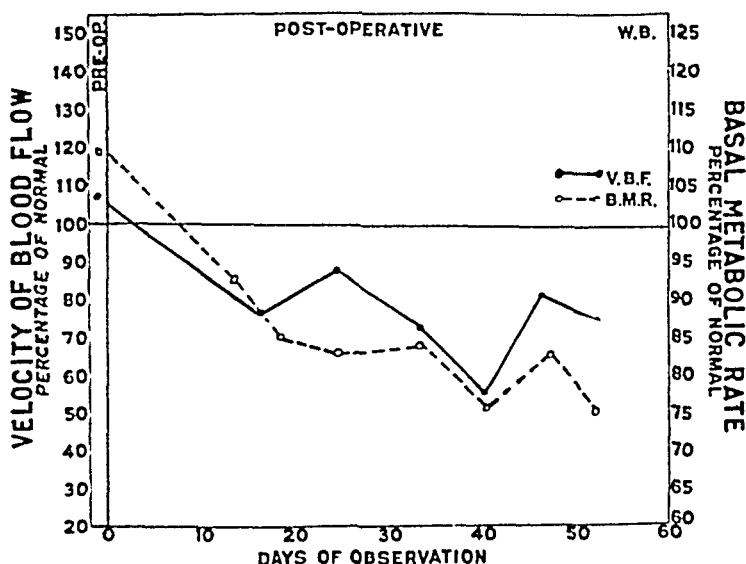


Chart 4 (case 4).—The relation between the velocity of blood flow and the basal metabolic rate.

voltage of the QRS complexes; the pulse rate gradually dropped from a rate of from 70 to 90 per minute to a level of from 60 to 70 per minute. Before operation the hemoglobin was 82 per cent (Sahli), and the red blood count was 4,620,000. During the next six weeks the hemoglobin gradually dropped to 73 per cent (Sahli) and the red blood count to 4,080,000. The level of the systolic blood pressure was approximately 25 mm. of mercury lower after operation. There was a definite increase in the vital capacity, with an average of from 500 to 600 cc. above the preoperative level, which varied from 2,100 to 2,700 cc. During the last eight days the vital capacity had varied from 3,150 to 3,350 cc. Exercise tests caused considerably less fatigue than was present before operation with the same amount of work.

*Comment.*—At the time of writing, four months after operation, this patient with arteriosclerotic heart disease, angina pectoris and cardiac asthma showed significant improvement. The attacks of paroxysmal dyspnea, pain in the chest and palpitation had disappeared. He had

been up and about for short periods during the day without dyspnea. Paralleling the clinical improvement there were a persistent lowering in the metabolic rate and a slowing in the velocity of blood flow. No significant symptoms of myxedema had developed, and his mind remained alert.

*CASE 5.—Arteriosclerotic heart disease and angina pectoris for eighteen months; attacks reproducible under standard conditions.*

A. B., a man, aged 57, a German laborer, was referred to the Beth Israel Hospital through the courtesy of Dr. Joseph H. Pratt on Feb. 21, 1933. The family and past histories were irrelevant. He had always been a strong and vigorous worker until about eighteen months before admission when, while digging a ditch, he suddenly experienced a severe squeezing pain in the substernal region which forced him to cease work. This passed off after a few seconds, but recurred every time he attempted to work. He therefore left his job and rested at home for four months, but on return to work the attacks recurred. The pain did not radiate, but was frequently associated with what he described as a "tired feeling in the arms." It was relieved within a few minutes by rest and also by the administration of glyceryl trinitrate. During the past year he had been unable to work. Substernal distress occurred regularly after he had walked a few blocks and was particularly more frequent in the winter. He was seen periodically in the clinic for cardiac diseases of the Boston Dispensary during this period and in spite of treatment continued to have the same attacks.

Physical examination revealed retinal sclerosis and moderate thickening of the peripheral vessels. The left border of cardiac dullness was within normal limits; the sounds were slow, regular and of good quality. There were no murmurs. The lungs were clear. The liver was not palpable. There was no peripheral edema. The blood pressure during the first week of admission was in the vicinity of 170 systolic and 100 diastolic; thereafter it ranged from 140 systolic and 84 diastolic to 124 systolic and 70 diastolic.

Laboratory tests showed no abnormalities. These tests included examinations of the urine, phenolsulphonphthalein renal function tests, red blood cell counts, white blood cell counts, determinations of the hemoglobin, examinations of blood smears, estimations of the nonprotein nitrogen in the blood and Wassermann, Kahn and Hinton tests of the blood. The venous pressure, velocity of blood flow and basal metabolic rates were within normal limits. An electrocardiographic tracing showed normal sinus rhythm with occasional ventricular premature beats. The P R and Q R S intervals and the T waves were normal. There was no Q wave in lead III. A roentgenogram of the heart taken at a distance of 7 feet revealed no enlargement.

*Exercise Tests.*—This patient was a stolid phlegmatic person who minimized his symptoms, but who, nevertheless, had been unable to work for over a year and was unable to walk any great distance without attacks of substernal pain. He remained in the hospital under observation for twenty-one days, and during this time he had no anginal attacks when at rest or while exercising indoors. When he was allowed to walk outdoors in cold windy weather, however, typical anginal attacks occurred under observation. It was found that after walking from one half to three fourths of a mile he was forced to stop because of a squeezing sensation in the substernal region. After fifteen seconds of rest he was able to continue, but thereafter the attacks were precipitated more readily and after walking shorter distances. A typical experiment of this sort is shown in table 1.

The length of time and the amount of exercise necessary to precipitate the attacks of angina were found to vary from day to day. In general, the attacks were less easily produced on warm days or when there was little wind. It was found possible to precipitate anginal attacks with a greater degree of constancy when the conditions were standardized by having the patient exercise in a room the temperature of which could be kept at a constant level. For this purpose a Barach oxygen chamber filled with ordinary air was used, the temperature being kept at from 48 to 56 F. The exercise consisted of repeatedly walking up and down a flight of 2 steps, each being 9 inches high. During the experiment the patient was dressed in hospital attire consisting of cotton flannel pajamas, a cotton bathrobe, cotton socks and felt slippers. After performing from 58 to 73 trips up and

TABLE 1.—*Experiment as Performed on Patient in Case 5*

Attack	Distance from Hospital, Miles	Time Elapsing Since Start, Minutes	Time Taken for Rest, Seconds
First... . .	0.5	7.5	15
Second.. .	0.6	9.5	15
Third.....	0.7	11.5	30
Fourth... . .	0.9	18.25	25
Temperature, 55 F.			
Total distance walked, 1.15 miles.			
Total time, twenty-three minutes			

TABLE 2.—*Comparison of the Production of Anginal Attacks Under Standard Conditions Before and After Operation*

Days Before Operation	Temperature of Room, F.	Patient's Weight, Pounds	Amount of Exercise, Trips	Work Performed, Ft.-Lbs.	Duration of Exercise, Minutes	Comment	Basal Metabolic Rate, Deviation from Normal, per Cent
29	56	141	65	13,750	4.4	Anginal attack	— 4
19	50	143	66	14,170	4.3	Anginal attack	— 9
18	50	143	58	12,450	3.8	Anginal attack	— 9
1	56	142	73	15,570	4.6	Anginal attack	— 5
Days After Operation							
12	50	139	142	29,600	10.0	No attack	—16
13	52	141	209	63,250	21.0	No attack	—16
23	48	144	207	44,700	15.0	No attack	—18
54	48	148	249	55,300	20.0	No attack	—18
48	52	152	383	81,600	30.0	No attack	—24

down the stairs under these conditions he was regularly forced to stop because of the development of angina pectoris. This experiment was repeated from day to day before operation and was found to give constant results.

*Further Course.*—The patient refused operation and returned home, but after fifteen days he returned because he found that he was unable to be up and about without precipitating substernal pain. Attacks of angina pectoris were precipitated under the same standard conditions employed before.

Total ablation of the thyroid gland was performed on April 1, 1933. Pathologic examination showed a normal gland.

The postoperative course was uneventful. The patient was allowed up nine days after operation; twelve days after the operation exercise in the cold room was repeated under precisely the same conditions as were previously employed. Angina, however, was not precipitated. Subsequently the patient was able to do more than

six times as much work as before operation without an attack of angina pectoris and without precipitating any discomfort other than slight dyspnea and moderate muscular fatigue incident to the amount of work performed (table 2). In fact, the test was terminated only because of fatigue.

Chart 5 shows the changes in the basal metabolic rates and the velocity of blood flow. The basal metabolic rate showed an immediate drop, reaching minus 18 per cent on the twenty-second day after operation. The velocity of blood flow also showed an initial slowing, but this was followed by a sharp unexplainable rise on the twelfth day after operation, followed by a drop which paralleled the drop in the basal metabolic rate.

The patient was discharged from the hospital on the fifteenth day after operation and returned for examination at frequent intervals. On May 19, the forty-eighth postoperative day, the basal metabolic rate was minus 24 per cent. The velocity of blood flow had begun to slow. Electrocardiographic tracings taken on the fifteenth and thirty-fifth days after operation showed a progressive diminution in the voltage

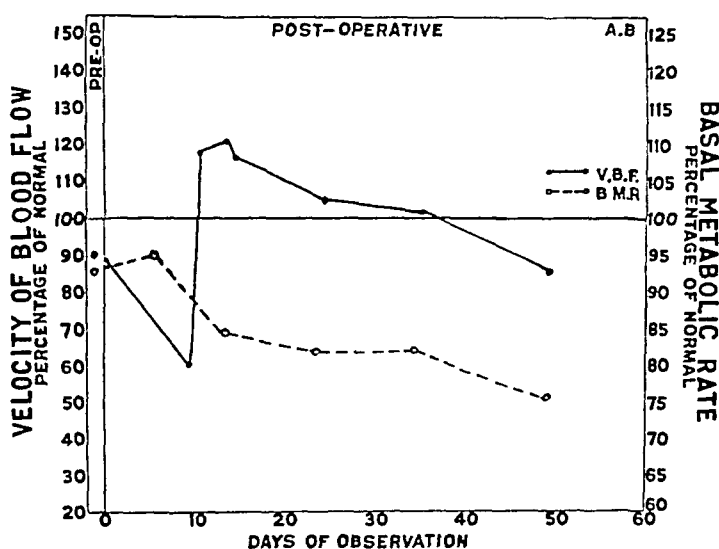


Chart 5 (case 5).—The relation between the velocity of blood flow and the basal metabolic rate.

of the Q R S complexes and an appreciable flattening of the T waves in all leads. The red blood count showed no change. The patient had been up and about, had performed light work and had not at any time experienced an attack of pain. Exercise tests, in which he was made to climb 766 steps in thirty minutes, were likewise unsuccessful in precipitating anginal attacks. His general condition was excellent, and he stated with enthusiasm that he was ready for work and looking for a job.

*Comment.*—This patient with a history of angina pectoris had attacks which were regularly reproducible after a given amount of exercise under standard conditions. At the time of writing, three and one-half months after operation, he had experienced no recurrence of cardiac pain. Repeated attempts to reproduce the attacks under the same standard conditions had failed, in spite of the fact that he had exercised almost to the point of exhaustion on repeated occasions.

CASE 6.—*Rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation, dyspnea and palpitation for twenty-three years; congestive failure for five years.*

B. Z., a housewife, aged 42, was first admitted to the Beth Israel Hospital on Oct. 15, 1932, complaining of palpitation, dyspnea and swelling of the legs of five years' duration. There was no history of rheumatic fever. In 1909, twenty-three years before entry, dyspnea and palpitation developed on exertion, and she coughed up blood; she was informed that she had heart trouble. In spite of slight dyspnea on exertion, she continued to work hard, married and had two children, twenty and sixteen years before admission, without the onset of congestive failure.

Approximately ten years before admission to the hospital attacks of palpitation and dyspnea, which had been very mild, became more severe and appeared after excitement and occasionally at night. Nocturnal attacks awakened her and were accompanied by dyspnea, orthopnea and vague pains in the precordial region. Pounding of the heart was distressing and persisted for from ten to fifteen minutes.

Five years before entry swelling of the ankles was noted for the first time, and three years before, edema of the legs became marked. Two years prior to admission, along with increasing cyanosis, dyspnea, palpitation and edema, the patient became orthopneic, and she noticed that the attacks of palpitation were accompanied by mild, nonradiating precordial pain which often persisted twenty-four hours or longer.

During the six months before entry the swelling of the legs, weakness, fatigue, dyspnea and palpitation became more pronounced. In spite of this, however, she continued to be up and about during the greater part of the day, but was finally forced to enter the hospital on October 15.

Physical examination showed a poorly nourished woman with moderate dyspnea and deep plum-colored cyanosis of the lips, malar prominences and tips of the fingers. With the patient sitting upright, the veins of the neck were moderately engorged. The heart was greatly enlarged, the apical impulse and left border of dullness being in the anterior axillary line. At the apex, systolic and diastolic thrills were palpable. The heart sounds were slow and absolutely irregular. At the apex the first sound was accentuated, and rough systolic and diastolic murmurs were heard. The blood pressure was 110 systolic and 70 diastolic. At the bases of both lungs there were moderate dullness and many coarse râles. The liver was greatly enlarged, reaching almost to the crest of the ileum. Deeply pitting edema of the lower extremities extended to the thighs and over the sacrum and back.

Examination of the urine and blood gave normal results except for albuminuria. The vital capacity of the lungs ranged from 1,100 to 1,700 cc. The basal metabolic rated varied from plus 4 to minus 5 per cent. The electrocardiogram showed auricular fibrillation, an inverted T<sup>1</sup> and marked right axis deviation. After the administration of digitalis, repeated venesection and intravenous injection of euphyllin (theophylline ethylenediamine) and salyrgan, the condition improved, diuresis occurred, and the patient lost 33 pounds (15 Kg.) of edema fluid. She was discharged fifty-one days after admission.

The patient returned home, limited her intake of fluids and salt, took a maintenance dose of digitalis and rested in bed all day, getting up only for meals and lavatory needs. The slightest departure from this regimen precipitated the symptoms and signs of congestive failure. As the patient was completely incapacitated in spite of all known medical treatment, total ablation of the thyroid gland was suggested. She was admitted to the hospital on April 3, 1933, for this procedure.



Physical examination showed slight dyspnea, orthopnea and intense plum-colored cyanosis of the lips, malar prominences and fingers. Examination of the heart gave essentially the same results as during the previous admission. At the base of the left lung there were numerous fine moist râles. The liver was non-tender, extending 4 fingerbreadths below the costal margin. There was slight pitting edema of the ankles and legs.

An electrocardiogram showed auricular fibrillation and marked right axis deviation. A roentgenogram of the heart taken at a distance of 7 feet showed great enlargement and a prominent shadow of the left auricle. The transverse diameter of the heart was 17.3 cm.; the transverse diameter of the chest, 26.4 cm. The vital capacity of the lungs varied from 1,700 to 1,880 cc. The venous pressure was 12 cm. of water. The basal metabolic rate ranged from minus 5 to minus 7 per cent. The arm to tongue circulation time varied from twenty-eight to thirty-two seconds.

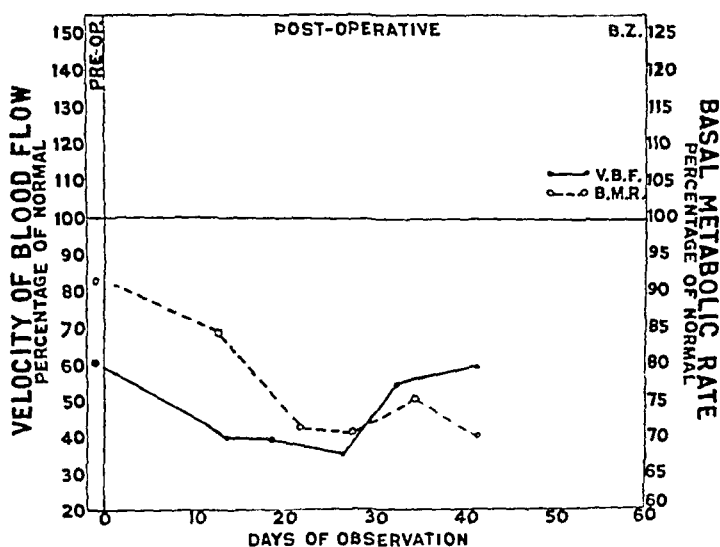


Chart 6 (case 6).—The relation between the velocity of blood flow and the basal metabolic rate.

The day preceding operation, examination of the chest revealed coarse and medium râles over both lungs posteriorly as high as the angle of the scapula.

On April 8 total ablation of the thyroid gland was performed with the patient under gas-oxygen anesthesia; the operation required one hour and thirty minutes. The thyroid gland was normal grossly and microscopically. The patient did well throughout the operation; the blood pressure varied from 90 systolic and 60 diastolic to 110 systolic and 70 diastolic, and the pulse rate, from 75 to 95 beats per minute. The postoperative course was smooth and uneventful, the temperature showing practically no rise. The respiratory rate increased from 20 to 30 per minute and continued at this level for four days, gradually returning to normal. Postoperative examination of the lungs showed râles over both lungs, but by the fourth day the right lung was entirely clear for the first time since admission. The signs on the left side had also diminished, with only a few medium-sized râles at the extreme base of the left lung. The patient was considerably calmer and remarked that she no longer felt "the pounding in her heart."

On the fourth postoperative day the patient complained of numbness and "pins and needles" sensations over the face and the distal ends of the extremities. Tests

for Chvostek's and Trousseau's signs were positive. One cubic centimeter of parathyroid extract-Collip was given immediately; 4 cc. of a 35 per cent solution of calcium chloride was given hourly, and 0.5 cc. of viosterol, 250 D, was given every six hours orally. After eight hours all symptoms had vanished. Trousseau's sign was absent, and Chvostek's sign was greatly diminished. No more parathyroid extract was given, and doses of calcium chloride were given only every three hours. The serum calcium concentration was normal throughout this time, the first analysis having been performed one hour after the institution of therapy. After seventy-two hours the serum calcium was 16 mg. per hundred cubic centimeters, and so all therapy was discontinued. On the eighth day calcium chloride therapy was again given because of a slight recurrence of symptoms. The patient felt well and was receiving calcium chloride in doses of 4 cc. three times a day.

She continued to improve, and remained unaware of her heart action. Dyspnea and cyanosis became obviously less marked. Chart 6 shows the changes in the basal metabolic rate and the velocity of blood flow. On the nineteenth day after operation the metabolism fell to minus 37 per cent, and the circulation time, which was prolonged to start with, became somewhat slower. Electrocardiograms showed no change. The vital capacity became slightly increased, the highest reading before operation being 1,800 cc. as compared with 2,150 cc. afterward. With the lowering of the metabolic rate, mild secondary anemia developed, the red count decreasing from 5,780,000 per cubic millimeter to 4,060,000; the hemoglobin dropped from 92 to 75 per cent on the twenty-seventh day after operation.

The patient's general improvement was striking. She was able to sleep soundly without orthopnea, and on the twentieth day after operation she was permitted to be up and about the wards. She took short walks without any evidence of shortness of breath and maintained that she had not felt so well for at least ten years. The liver was no longer palpable, and except for an occasional râle at the base of the left lung there were no signs of congestive failure.

An interesting result of operation has been her increased calmness. Although a cooperative patient, she was very sensitive and easily excited, her apical rate often rising 60 beats above the basal level at the mere approach of the visiting physician. Since operation, this excitability has conspicuously lessened.

*Comment.*—At the time of writing, three and one-half months after operation, this patient with rheumatic heart disease and signs of circulatory failure of twenty-three years' duration showed conspicuous improvement. Palpitation and dyspnea on slight exertion had disappeared. She was able to lie flat in bed without distress. Cyanosis, which was striking before operation, had become appreciably less, and she had shown steady improvement even after being up and about for two and one-half months. The basal metabolic rate had decreased, and the velocity of blood flow had correspondingly slowed.

*CASE 7.*—*Hypertensive heart disease, attacks of cardiac asthma for two years; conspicuous improvement after operation; sudden attack of pulmonary edema, and death twenty-one days after operation.*

W. L., an ex-bartender, 60 years of age, was admitted to the Beth Israel Hospital on March 23, 1933, complaining of shortness of breath of two years' duration. The past history was unimportant. The present illness began two years before entry with sudden attacks of coughing and difficulty in breathing which lasted from fifteen to twenty minutes. At the same time he noticed short-

ness of breath on exertion, and while driving his car he often experienced sudden spells of breathlessness. One year before admission the symptoms became more pronounced and more frequent. The attacks were not attended with pain and rarely occurred at night. Six weeks before admission he was forced to go to bed because of attacks repeated two or three times a day. Despite several weeks of rest the symptoms continued. Five days before admission he was seized with an unusually severe attack which lasted for about an hour and was accompanied by wheezing and marked prostration. At this time moderate swelling of the legs and some swelling of the right hand developed. Because the paroxysmal attacks of dyspnea continued in spite of all medical treatment he was referred to the hospital.

Physical examination revealed a swarthy, somewhat pale, lethargic man propped up in bed in respiratory distress with cyanosis of the lips and cheeks. The retinal vessels were narrowed and sclerosed. Percussion revealed enlargement of the heart, the left border being 10 cm. to the left of the midsternal line. The sounds were slow and regular. There were a systolic murmur at the apex and a rough systolic murmur at the aortic area. The blood pressure was 220 systolic and 90 diastolic. At the bases of both lungs and in the left anterior axillary region fine and medium moist râles were heard. The liver was enlarged to 4 fingerbreadths below the costal margin. There were clubbing and cyanosis of the tips of the fingers. There was no clinical evidence of thyrotoxicosis.

The urine contained a slight trace of albumin, and the specific gravity varied from 1.010 to 1.022. The greatest excretion of phenolsulphonphthalein in two hours and ten minutes was 25 per cent in five successive tests. The red blood count was 3,950,000 per cubic millimeter; the hemoglobin was 65 per cent, and the white blood cells numbered 18,400, with a normal differential count. A roentgenogram of the heart taken at a distance of 7 feet showed transverse enlargement of the heart with prominence of the left ventricle. The transverse diameter of the heart was 16.1 cm.; the transverse diameter of the chest was 28.7 cm. An electrocardiogram showed normal sinus rhythm, the rate being 70, inverted T waves in all three leads and a P R interval of 0.25 second. The vital capacity of the lungs on admission was 1,200 cc.; this gradually rose to 2,300 cc. before operation. The venous pressure varied from 7 to 8 cm. of water. The velocity of blood flow was slowed; the arm to tongue circulation time varied from thirty to thirty-one seconds. The basal metabolic rate was plus 21 per cent, plus 24 and plus 21 per cent on three different days.

During the first twenty-four hours after admission the patient had several brisk attacks of paroxysmal dyspnea requiring morphine for relief, but during the next three days the attacks became less frequent and less severe. Gallop rhythm was noted on many examinations, and moist râles persisted at the bases of both lungs.

On April 11 total ablation of the thyroid gland was performed with the patient under gas-oxygen anesthesia, the operation requiring two hours. The patient's general condition was excellent throughout. The blood pressure did not rise above 220 systolic and 90 diastolic. The pulse rate varied from 100 to 130. The temperature rose to 103.5 F. on the first day after operation, returning to normal the next day. The pulse returned to normal on the fourth day after an initial rise to 120.

Pathologic examination of the thyroid gland showed a quiescent colloid nodular goiter. There was cystic degeneration of a removed parathyroid glandule.

The patient made a good recovery and was quite cheerful and talkative a few hours after the operation. He continued to be in excellent spirits, minimizing any

discomfort and maintaining that he felt better. His voice was husky for a few days, but both cords moved well. Examination of the lungs revealed a moderate number of medium and crackling râles at the bases of both lungs, extending as high as 3 fingerbreadths below the angle of the scapula.

Three days after operation the râles at the bases of both lungs had considerably diminished. Seven days after operation the patient insisted that his mind was considerably clearer than before operation. He said that before operation he was "dead" and hardly knew that he was in a hospital. He took a lively interest in everything and appeared much improved. On the twelfth day after operation he was permitted to get out of bed and gradually increase his activity. He then noticed that there was considerably less palpation on exertion than he had experienced before operation. Walking up and down the corridor briskly caused no perceptible dyspnea. He regained strength and gained 6 pounds (2.7 Kg.). The vital capacity was in the vicinity of 2,150 cc. each day. The metabolic rate dropped from a level of plus 21 per cent to minus 4 per cent on the fifteenth day after operation. The velocity of blood flow showed a slight slowing at this time.

The patient continued to improve. His mind became clearer, orthopnea disappeared entirely, and the cyanosis diminished. He was up and about the wards without dyspnea or discomfort. The râles disappeared from the bases of both lungs, the liver could no longer be felt, and he stated that he had not felt so well for five years. His wife corroborated this statement and was enthusiastic over his improvement. The blood pressure continued to be elevated at 220 systolic and 110 diastolic.

On the twenty-first day after operation at about 10:00 p. m., the patient suddenly experienced paroxysmal dyspnea; he became acutely orthopneic and began to cough up large amounts of bloody froth. There was no pain. The blood pressure rose to over 300 systolic (the manometer used recorded only to 300 mm.). His condition of intense dyspnea with the coughing up of large amounts of frothy bloody sputum continued. Morphine, tourniquets applied to the extremities, venesection, intravenous injections of dextrose, an oxygen tent and, finally, intracardiac injections of epinephrine and a Drinker respirator were employed without effect. The patient died two hours after the onset of the attack.

Autopsy showed a large heart weighing 660 Gm., with marked hypertrophy of the left ventricle. The lungs showed chronic passive congestion throughout with additional pulmonary edema in the upper lobes. There was bilateral hydrothorax of 500 cc. in each cavity.

*Comment.*—This patient with hypertensive heart disease and attacks of cardiac asthma increasing in severity during the two years before operation showed striking improvement after thyroidectomy. His palpitation and respiratory distress disappeared; râles that had been present at the bases of both lungs entirely cleared; cyanosis diminished, and his mind became clearer than it had been before operation. He regained strength, was able to walk briskly up and down the corridor without dyspnea and stated that he had not felt so well for five years. On the twenty-first day after operation, however, after being out of bed the entire day for ten days, he suddenly experienced an attack of pulmonary edema and in spite of all efforts died two hours later.

*CASE 8.*—*Rheumatic heart disease, mitral stenosis and insufficiency and dyspnea for fourteen years; hemoptysis and congestive failure for one year.*

W. D., an American, aged 23, a bus boy, was admitted to the Beth Israel Hospital on April 11, 1933, complaining of shortness of breath on exertion, fourteen years in duration. There was no history of rheumatic fever. The present illness began at the age of 9 when he was referred to the Lawrence General Hospital. Physical examination at that time showed the characteristic thrill and murmurs of advanced mitral stenosis and insufficiency. He remained in bed for six weeks, but on attempting to resume normal life found that the usual activities of childhood caused him to become very short of breath. At the time he was conscious of a choking sensation and pain in the region of the heart which often radiated to the left shoulder. During the next thirteen years there was only a slight increase in symptoms. Thirteen months previously, however, he suddenly began to cough up large amounts of blood, averaging three cupfuls daily for several days. During this attack he was sent to the Boston City Hospital, where he remained in bed for six weeks. He returned home and was fairly comfortable, spending the greater part of the day in bed. The slightest departure from this regimen, however, caused severe dyspnea. For this reason he was transferred to a hospital for chronic diseases where, except for occasional attacks of hemoptysis, he was fairly comfortable for three months, following which he again had intense dyspnea, orthopnea and palpitation which persisted for three and a half months. When seen in February, 1933, he was considered too sick for any operative procedure. On continued rest in bed his condition improved somewhat, and he was transferred to the Beth Israel Hospital for study and operation.

Physical examination showed good development, mental alertness, slight dyspnea, orthopnea and cyanosis of the cheeks, nose and lips. The left anterior part of the chest showed a marked bulging deformity. A diastolic thrill was palpable at the apex, and the impulse was seen and felt in the fifth space 10 cm. from the midsternal line. The sounds were slow and regular; the first sound, at the apex, was loud and booming; the second pulmonic sound was accentuated. There were a loud rumbling crescendo diastolic murmur and a loud blowing systolic murmur in the mitral area. The lungs were clear throughout. The blood pressure was 110 systolic and 72 diastolic.

Examinations of the urine and blood gave normal findings. A roentgenogram taken at a distance of 7 feet showed moderate cardiac enlargement, the transverse diameter being 17.8 cm.; the internal diameter of the chest was 30 cm. An electrocardiogram showed sinus rhythm with auricular premature beats, large and notched P waves in leads I and II, a P R interval of 0.22 second and right axis deviation. The venous pressure was approximately 5 cm. of water; the arm to tongue circulation time by the decholin method varied from fifty to fifty-two seconds; the basal metabolic rate was minus 8 per cent.

On the day preceding operation, with the patient semirecumbent, there were cyanosis of the face and engorgement of the veins of the neck, and a distinct protodiastolic gallop rhythm was noted at the apex. There was Cheyne-Stokes respiration. The liver was palpable on deep inspiration, and the edge was definitely tender. There was slight pitting edema of the legs.

Total ablation of the thyroid gland was performed on April 15 with the patient under gas-oxygen anesthesia; the operation required two hours and twenty-two minutes. Just before operation the patient appeared excited. The heart rate was 94, and on palpation of the radial pulse there was definite pulsus alternans; this observation was corroborated by measurements of the blood pressure. During the course of operation the pulsus alternans disappeared. The blood pressure varied from 110 systolic and 80 diastolic to 105 systolic and 80 diastolic; the pulse rate ranged from 120 to 100. Fifteen minutes after operation the patient talked. His lungs were clear, and his general condition was excellent.

The next day a few medium and fine crackling râles were heard at the bases of both lungs. Except for two transient rises to 100 F., there was practically no elevation in the pulse or the temperature following the operation.

The following notes were made by the resident physician:

April 19 (four days after operation): The patient is feeling comfortable. It is too early to judge the effects of operation.

April 26 (eleven days after operation): The patient volunteers that he no longer has the pounding in his chest that was always present before operation. He is considerably more alert and more given to smiling than at any previous time.

On the second postoperative day there was a slight Chvostek sign on the left side of the face which continued to be present occasionally during the next ten days. The patient was given 8 cc. of a 35 per cent solution of calcium chloride four times a day and once at night, and 0.5 cc. of viosterol twice a day. Chart 7 shows the changes in the basal metabolic rate and the velocity of blood flow. The

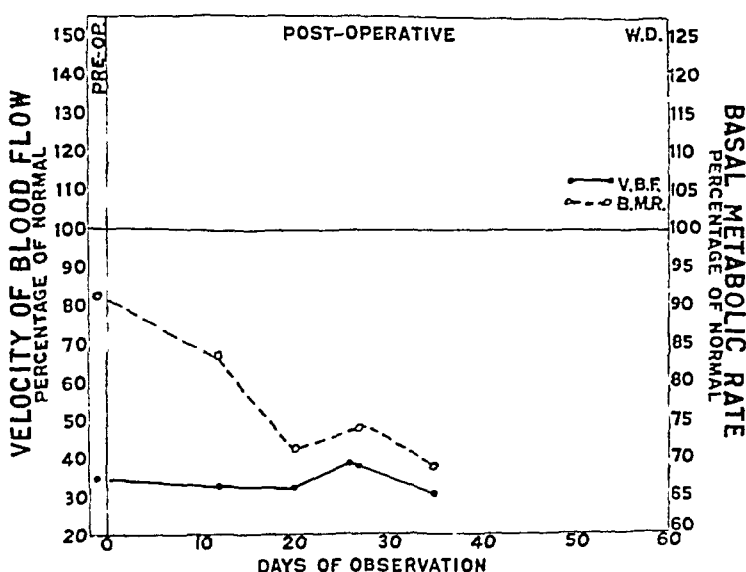


Chart 7 (case 8).—The relation between the velocity of blood flow and the basal metabolic rate.

basal metabolic rate fell rapidly, reaching minus 30 per cent on the twentieth day after operation. The arm to tongue circulation time, which had been prolonged to fifty-two seconds on admission, became fifty-seven seconds on the twentieth postoperative day.

Successive electrocardiograms showed a definite flattening of the T waves, particularly in lead I. The voltage of the Q R S complexes showed no appreciable change. There was a successive increase in the P R interval from 0.20 second before operation to 0.25 second one month after operation. The vital capacity showed a definite rise of approximately 400 cc. above the preoperative level, the highest reading before operation being 2,400, and that after operation, 2,800 cc. The red blood count showed no change, being 5,430,000 six weeks after operation.

The patient slept soundly. Although he still preferred one or two pillows at night, he could lie perfectly flat without discomfort. Breathing was notably easier. On the twelfth day after operation he was permitted out of bed. At the time of writing he had been up and walking without dyspnea or fatigue for one month. There had been no hemoptysis.

Repeated exercise tolerance tests showed marked improvement. There were considerably less dyspnea and fatigue, and the pulse returned to its resting level within one-half the time recorded in the preoperative performances. Whereas the preoperative tests caused the blood pressure to fall after exercise, the tests made after operation showed the normal sharp rise.

The patient stated that he was more comfortable and felt better than he had at any time during the preceding three years.

*Comment.*—At the time of writing, three months after operation, this patient with rheumatic heart disease, dyspnea of fourteen years' duration and attacks of congestive failure of one year's duration showed conspicuous improvement. Palpitation, orthopnea and dyspnea had disappeared. During the past month he had walked from 2 to 3 miles a day without fatigue, dyspnea or any evidence of congestive failure. Parallel-ing this improvement, the basal metabolic rate dropped to minus 30 per cent and remained low.

*CASE 9.—Rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation and attacks of congestive failure for twenty-six years.*

L. B., a Canadian housewife, aged 45, was referred to the Beth Israel Hospital on April 12, 1933, through the courtesy of Dr. Otto C. Yens. Shortness of breath had been present for thirty-two years. She had diphtheria at the age of 7 and never quite recovered her full strength. At the age of 12 she had rheumatic fever with symptoms in the joints persisting for three months; since then shortness of breath and palpitation on slight exertion had always been present. She was able to go to school, however, and later did light work, but always was conscious of her physical limitations. At the age of 19, twenty-six years before admission, she had a severe attack of epistaxis, and one year later she was forced to bed with marked palpitation, dyspnea and moderate edema of the extremities. Several weeks were spent at a convalescent home, but when she returned home dyspnea and palpitation reappeared. Each year, from 1909 to 1927, she had dyspnea and edema of the legs. Following pneumonia in 1927 orthopnea became significant, and from that time on dyspnea and palpitation on exertion was so pronounced that the patient was unable to spend more than two or three hours a day out of bed. During the past ten years she had a more or less continuous pressure and a dragging sensation in the left anterior part of the chest and sharp pain on exertion. Edema had been less marked during the last five years, although it was present most of the time.

Physical examination in the hospital, after the patient had been completely at rest in bed at home for a month, revealed a pale, well developed, middle-aged woman propped up in bed with slight dyspnea and with moderate cyanosis of the lips, nose and cheeks. The veins of the neck and arms were moderately engorged with the patient in the upright position. The apex impulse was felt at the sixth interspace in the anterior axillary line. The heart sounds were slow and absolutely irregular; the first sound at the apex and the second pulmonic sound were accentuated. The ventricular rate was 68. A rumbling diastolic murmur and a harsh blowing systolic murmur were heard in the mitral area. The lungs were clear. The blood pressure was 140 systolic and 80 diastolic. The edge of the liver was nontender and barely palpable. There was slight pitting edema of the tibiae.

Examination of the urine gave normal results. There was slight secondary anemia, the red blood count being 4,290,000 and the hemoglobin 77 per cent. A

roentgenogram of the chest taken at a distance of 7 feet showed the transverse diameter of the heart to be 13.9 cm. and the internal diameter of the chest 22 cm. The right auricle was prominent. An electrocardiogram showed auricular fibrillation with a slow ventricular rate, erect T waves in leads I and II and right axis deviation. The vital capacity of the lungs varied from 1,750 to 1,850 cc., the venous pressure, from 10 to 12 cm. of water. The arm to tongue circulation time ranged from seventeen to nineteen seconds; the basal metabolic rate was minus 10 per cent.

On April 17, total ablation of the thyroid gland was performed with the patient under gas-oxygen anesthesia; the operation required one hour and thirty minutes. The patient's condition remained excellent throughout. The blood pressure did not rise above 120 systolic, nor the pulse above 90 per minute. There was practically no postoperative reaction, the temperature being 100 F. on the second day, with a return to normal on the third day after operation.

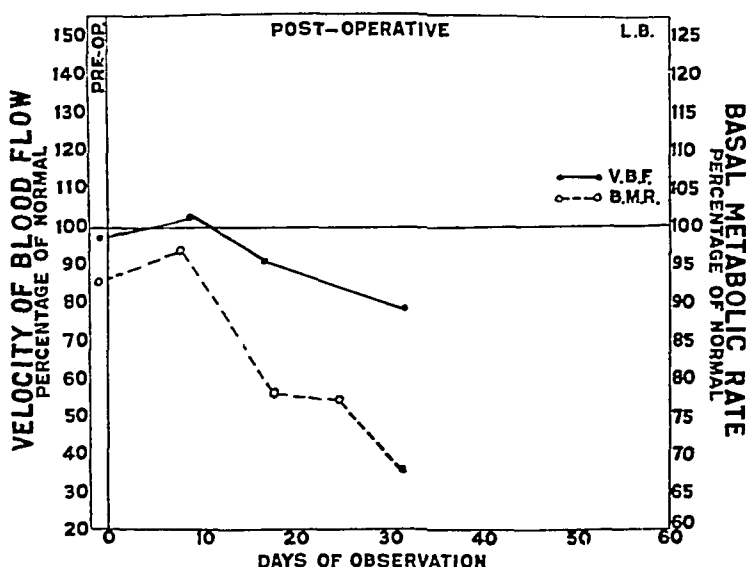


Chart 8 (case 9).—The relation between the velocity of blood flow and the basal metabolic rate.

On the seventh postoperative day the patient stated that she felt considerably easier and volunteered that there was much less palpitation with a change in position. This symptom had been constant for years before operation. She noticed that she was able to breathe easier and that she could sleep on the left side, something she had been unable to do for six years; she used fewer pillows at night. The following routine notes were made by the resident physician:

May 5 (eighteen days after operation): During the past ten days there has been a definite change in the patient's appearance and general attitude. She is more calm, looks more rested and complains less frequently. She states and demonstrates that she is able to move about quite freely without the return of palpitation.

May 12: The patient has increased her activities and has been up and about in a wheel chair without noticing fatigue. Breathing has continued to improve without evidence of dyspnea in the course of getting in and out of bed. Orthopnea is definitely less marked than it was one week ago, although she still sleeps in a semirecumbent position. Other than a slight dull pain in the region of the precordium which was present on awaking this morning and which persisted for ten



minutes, there has been no return of the preoperative pain which had been constant for years.

Chart 8 shows the changes in the basal metabolic rate and the velocity of blood flow. On the eighteenth day after operation the metabolism had fallen to minus 22 per cent, and the arm to tongue circulation time was prolonged. Electrocardiographic tracings made fifteen days after operation showed appreciable flattening of the T waves and a decrease in the voltage of the Q R S complexes. The vital capacity showed a slight but persistent increase, the highest reading before operation being 1,850 cc., and that after operation, 2,050 cc. The red blood cell count and hemoglobin showed no appreciable change. An exercise test performed before operation resulted in marked dyspnea, prostration and almost collapse when less than half the standard amount of work was performed. Thirty-two days after operation the same amount of exercise was accomplished without discomfort and with very slight dyspnea; the blood pressure returned to the resting level within two minutes, compared with nine and a half minutes before operation. The patient continued to improve and was able to be up and about without dyspnea or fatigue. The pressure pain in the region of the heart that was continuous for more than ten years before operation disappeared. The patient stated that she had not felt so well at any time during the preceding six years.

*Comment.*—Three months after operation, this patient with rheumatic heart disease and attacks of congestive failure of twenty-six years' duration showed striking improvement. Palpitation, dyspnea and orthopnea had disappeared. She was able to be up and about without signs of congestive failure. Before operation a standardized amount of exercise almost precipitated collapse, but at the time of writing the patient was able to perform the same exercise with little or no dyspnea and with a more normal response of the pulse and blood pressure. Corresponding to the clinical improvement the basal metabolic rate became lowered and the velocity of blood flow prolonged.

*CASE 10.*—*Bronchial asthma for twenty-nine years; erythrocytosis, cor pulmonale and right ventricular heart failure with edema for five years.*

F. C., a man, 31 years of age, was transferred from the Massachusetts General Hospital through the courtesy of Dr. James H. Means on April 13, 1933. He gave a history of bronchial asthma twenty-nine years in duration. At the age of 2 a generalized eczematous rash and attacks of wheezing developed. These attacks occurred weekly up until the age of 9, when they became more severe, necessitating the upright position during sleep. Between the age of 10 and 20 years attacks occurred approximately two or three times a week and generally awoke him out of a sound sleep. This continued until five years prior to admission, when the attacks became less frequent and severe. About that time, however, he noticed that he was always short of breath on exertion. In 1929 dyspnea suddenly increased, and widespread edema developed on the legs, trunk and face. There was moderate palpitation of the heart but no pain in the chest. The patient was sent to the Massachusetts General Hospital, where he remained for several months; under the influence of diuretics he lost 54 pounds (24.5 Kg.). He returned to work with restricted activity, but after a few months again had dyspnea on exertion and edema of the legs. He was admitted to the Massachusetts General Hospital four times, the interval between successive admissions becom-

ing progressively shorter. After the third admission he returned home and, except for one hour daily, was confined to bed. In spite of this rest, shortness of breath and moderate edema of the legs recurred, necessitating his return to the hospital after only seventeen days at home. Asthmatic attacks had occurred daily. During this admission it was the opinion of Dr. Means that the patient's reserve was so limited that he would be a cardiac invalid the remainder of his life. He therefore placed the possibility of total ablation of the thyroid gland before the patient for decision, clearly stating its experimental nature.

Physical examination on admission to the Beth Israel Hospital after six weeks of rest in bed at the Massachusetts General Hospital revealed a dark-skinned, conspicuously cyanotic young man with moderate respiratory distress. The chest was definitely emphysematous; there was narrowing of the costal angle on inspiration. The cardiac apex was barely felt in the fifth intercostal space just within the nipple line. The left border of dullness was 9.5 cm. from the midsternal line.

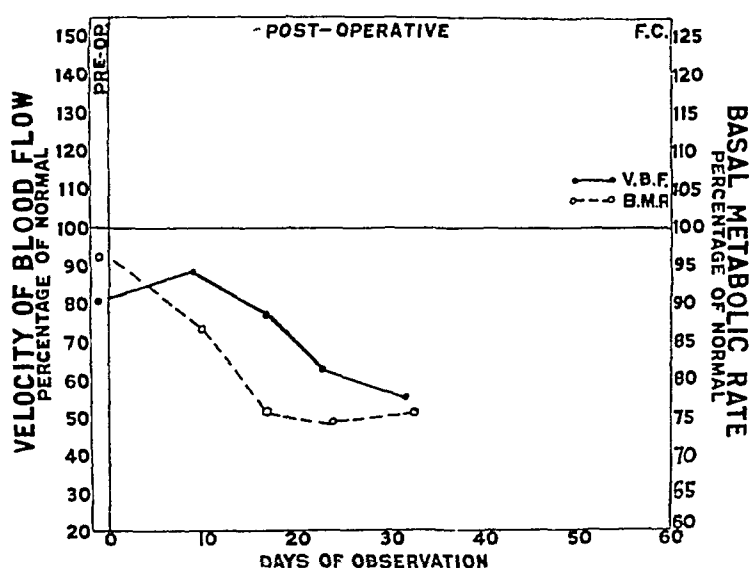


Chart 9 (case 10).—The relation between the velocity of blood flow and the basal metabolic rate.

The sounds were slow, regular and of good quality. There were no murmurs. The blood pressure was 120 systolic and 70 diastolic. The lungs were hyperresonant to percussion, and at the bases numerous crackles and sibilant rhonchi were heard. The edge of the liver was not felt. There was no edema of the extremities.

Examination of the urine gave normal results. The red blood cell count was 6,420,000 per cubic millimeter; the hemoglobin was 89 per cent; the white blood count was 8,500, and the smear was normal. A roentgenogram of the heart taken at a distance of 7 feet showed slight enlargement, especially to the right, the transverse cardiac diameter being 15.1 cm.; the internal diameter of the chest was 27.1 cm. An electrocardiogram showed a normal sinus rhythm, a ventricular rate of 80, inverted T waves in leads II and III, a P R interval of 0.20 second and right axis deviation. The vital capacity of the lungs varied from 1,900 to 2,400 cc.; the venous pressure, from 4 to 6 cm. of water, and the arm to tongue circulation time, from twenty to twenty-three seconds. The basal metabolic rate was found to vary between minus 5 and minus 2 per cent.

On April 18, 1933, total ablation of the thyroid gland was performed. The patient's condition was excellent throughout the operation. The blood pressure

varied from 120 systolic and 100 diastolic to 130 systolic and 90 diastolic. The pulse rate remained below 105. After operation the temperature rose to 101 F., the pulse rate to 120 and respiratory rate to 35. After the third postoperative day the temperature, pulse and respirations were normal.

Slight hoarseness was present after the operation, but the vocal cords appeared normal. On the fourth day the patient stated that the pounding of his heart which had been present before operation had become appreciably less. The cardiac rate gradually slowed from 88 to 70 per minute. The cough diminished, but the pulmonary signs showed no change. On the eighth postoperative day the patient stated: "My breathing is much better now than it was before the operation. I used to have an asthmatic attack every damp day and that would continue until the damp weather ended. I have not had an attack since the operation." He noted that before operation he could not lie flat without a choking sensation, whereas after operation he preferred to sleep almost completely recumbent without discomfort. During the two weeks previous to the operation he had five asthmatic attacks. In spite of damp weather during twenty-nine days after operation, there was not the slightest wheezing. On May 17 and 18, one month after operation and during the season when the paroxysms had been most severe, he had two mild spells of wheezing which persisted for a few minutes and caused him little or no discomfort. He sleeps soundly without orthopnea. The vital capacity of the lungs increased from 2,400 to 3,100 cc. on the fourteenth day after operation. This level was sustained for five days, after which there was a decrease, the vital capacity still remaining about 300 cc. above the preoperative level. Chart 9 shows the changes in the basal metabolic rate and the velocity of blood flow. The basal metabolic rate showed a fall to minus 24 per cent on the sixteenth day. The velocity also slowed. The red blood count and hemoglobin were unchanged. An electrocardiogram showed a decrease in the height of the T wave in all leads.

The patient was permitted out of bed on the seventh day after operation. At the time of writing, somewhat over a month after operation, he had been on his feet the entire day for three weeks without any evidence of circulatory insufficiency. Exercise tolerance tests showed a striking improvement since operation. On May 19, one month after operation, he was able to perform twice the amount of work performed before without dyspnea or fatigue. He was able to perform the standard exercise tolerance test with a normal return of the blood pressure and pulse to the previous basal level within two minutes.

Dr. James H. Means, under whose care the patient had been at the Massachusetts General Hospital and who saw the patient on May 1, 1933, the thirteenth postoperative day, made the following note: "In my opinion, this is a remarkable result. I have known the patient for several years and his appearance is now unlike anything I have seen in him before. He is far less cyanotic and is really without dyspnea or orthopnea. His pulse is only 78 after walking around the ward. Of course, if his asthma becomes bad again he may get into trouble. Nevertheless, there is no doubt in my mind that his outlook in general has become vastly improved by the thyroidectomy."

The patient maintained that he felt better than at any time during the preceding seven years.

*Comment.*—This patient with cor pulmonale and congestive failure of five years' duration occurring as a result of long-standing bronchial asthma and chronic pulmonary emphysema showed significant improvement after thyroidectomy. Palpitation and dyspnea disappeared, and

he slept soundly in the recumbent position. He was able to perform more work without dyspnea or fatigue than was possible before operation. His attacks of bronchial asthma have become strikingly less frequent and less severe. Clinical improvement paralleled the fall in the basal metabolic rate and the changes in the velocity of blood flow.

CASE 11.—*Résumé of findings in case 3 (G. F.) of a previous communication<sup>1</sup> with report of the subsequent clinical course. Rheumatic heart disease, mitral stenosis, auricular fibrillation, angina pectoris and congestive failure for three years prior to operation. Clinical course six months following operation.*

G. F., a man, aged 52, an unemployed chef, entered the hospital complaining of shortness of breath, palpitation, substernal pressure and weakness of three years' duration. At the age of 12 he had rheumatic fever which forced him to remain in bed for three months. After this, however, he felt quite well until three years prior to examination, when while working he suffered an attack of severe precordial pain which radiated down both arms to the tips of the fingers. He became extremely dyspneic and was forced to remain in bed for three days. He returned to work, but two and a half months later was again forced to stop and enter a sanatorium because of increasing dyspnea. After a few months of rest he felt well except for a sense of substernal pressure, but on attempting to work he became short of breath and was again forced to go to bed. Dyspnea and attacks of substernal pain gradually became more and more severe in spite of the fact that he refrained from work and rested the greater part of the day. The attacks of substernal pain appeared frequently and were not necessarily brought on by effort; they appeared while the patient was at rest and sometimes during sleep. They lasted for several minutes and were regularly relieved by the administration of glyceryl trinitrate; during a period of prolonged rest in bed they were absent. For two years before admission he had gradually increasing edema of the legs, and during the last few months this was present every time he spent a few hours on his feet, in spite of prolonged rest in bed.

Physical examination on admission, after complete rest in bed for many months, showed orthopnea, slight cyanosis of the lips and mucous membranes, marked enlargement of the heart, grossly irregular heart sounds and a faint middiastolic murmur below and to the left of the nipple; there was no aortic diastolic murmur. The liver was enlarged and tender, there was definite pitting edema of the legs and sacrum, and scattered moist râles were heard over the bases of the lungs. The diagnosis was auricular fibrillation, congestive heart failure, mitral stenosis, regurgitation and, probably, old healed coronary thrombosis.

Total ablation of the normal thyroid gland was performed on Dec. 15, 1932, and the patient had an uneventful convalescence. The basal metabolic rate fell gradually, reaching minus 14 per cent two weeks after operation and minus 28 per cent four weeks after operation. The change in the clinical condition was conspicuous. The patient was no longer orthopneic; his craving for water entirely disappeared, and he failed to show any evidence of edema. He was able to undertake moderate exercise without dyspnea or signs of congestive failure, whereas before operation even combing his hair, or turning over in bed caused violent palpitation. He stated that for the first time in three years he was unaware that he had a heart. The sense of thoracic compression with numbness and occasional pain in the left arm did not reappear, and in spite of the lowered metabolism and somewhat increased sensitivity to cold his mental processes became more acute than they were prior to operation.

TABLE 3.—*Summary of the Effects of Total Ablation*

Diagnosis	Duration of Cardiac Decompensation	Before and Days After Operation	Basal Metabolic Rate, Percentage Deviation From Normal	Arm to Tongue Circulation Time, Seconds	Dyspnea	Orthopnea†	Palpitation	Cardiac Pain
Rheumatic heart disease; mitral stenosis and insufficiency	5 years	Before	+ 5	23	Moderate at rest	Intense	Intense at rest	Almost constant
		48 days	—22	45	Slight on exertion	Absent	Absent on exertion	Absent
Rheumatic heart disease; mitral stenosis; aortic insufficiency; auricular fibrillation; extreme cardiac enlargement; pulmonary and renal infarction	12 years	Before	— 3	42	Slight at rest	Intense	Intense at rest	Constant
		52 days	—30	66	Slight on exertion	Absent	Absent on exertion	Absent except with pulmonary edema
Arteriosclerotic heart disease	6 years	Before	+ 9	32	Intense on exertion	Slight	Constant at rest	Slight
		17 days	—23	68	Slight on exertion	Absent	Absent on exertion	Absent
Arteriosclerotic heart disease; hypertension; angina pectoris; cardiac asthma; Paget's disease	2 years	Before	+11	17	Intense on exertion	Slight	Absent	Absent
		43 days	—24	24	Slight on exertion	Absent	Absent	Absent
Arteriosclerotic heart disease; angina pectoris	18 months	Before	— 9	22	Absent	Absent	Absent	Absent
		48 days	—24	21	Absent	Absent	Absent	Absent
Rheumatic heart disease; mitral stenosis and insufficiency; auricular fibrillation	5 years	Before	— 6	30	Moderate at rest	Moderate	Intense at rest	Moderate
		41 days	—30	31	Slight on exertion	Absent	Slight on exertion	Absent
Hypertensive heart disease; cardiac asthma	2 years	Before	+21	30	Moderate at rest	Moderate	Moderate on exertion	Absent
		15 days	— 4	30	Slight on exertion	Absent	Absent	Absent
Rheumatic heart disease; mitral stenosis and insufficiency	13 months	Before	— 8	52	Slight at rest	Intense	Intense	Slight
		34 days	—32	58	Moderate on exertion	Slight	Absent	Absent
Rheumatic heart disease; mitral stenosis and insufficiency; auricular fibrillation	26 years	Before	—10	19	Slight at rest	Intense	Intense	Intense
		32 days	—32	23	Moderate on exertion	Slight	Slight	Slight
Cor pulmonale; asthma 29 years	5 years	Before	— 5	23	Moderate at rest	Intense	Moderate	Absent
		31 days	—24	32	Slight on exertion	Absent	Absent	Absent

\* On the twenty-first day after operation, pulmonary edema developed in the patient, and he died two hours after the onset.  
† Observations of orthopnea were made at the time of admission, whereas measurements of venous pressure were made

*of the Thyroid on Various Aspects of the Circulation*

Cough	Hem- optysis	Miscellaneous Symptoms	Peripheral Edema	Râles	Hepatic Enlarge- ment	Cyanosis	Heart Rate, Beats per Minute	Respira- tory Rate, per Minute	Blood Pressure, Mm. Hg	Vital Capacity, Cc.	V C
Intense	Almost daily	.....	Slight at rest	Present at base of left lung	Slight	Slight	72-100	20-36	100/60	3,500 to 3,600	
Absent	Absent	.....	Absent on activity	Absent	Absent	Absent	80-90	20	100/64 to 120/74	3,000 to 3,250	
Moder- ate	Fre- quent	Occasional attacks of pulmonary infarction	Absent at rest	Present at bases of both lungs	Absent	Absent	70-90	20-30	104/70 to 120/70	2,800 to 3,100	
Absent	Absent	Three attacks of pulmonary infarction	Absent on activity	Absent	Absent	Absent	50-60	20	120/70	2,900 to 3,350	
Intense	Absent	.....	Absent at rest	Absent	Absent	Absent	50-60	20-24	130/60 to 110/70	2,700 to 3,300	
Slight	Absent	.....	Absent on activity	Absent	Absent	Absent	50-60	20	120/70	3,700 to 3,950	
Absent	Absent	.....	Absent at rest	Absent	Absent	Absent	70-90	20-24	180/110 to 150/70	2,100 to 2,700	
Absent	Absent	.....	Absent on activity	Absent	Absent	Absent	60-70	20	140/90	3,150 to 3,350	
Absent	Absent	Angina pectoris on exertion	Absent	Absent	Absent	Absent	70-80	20	140/70	3,000	
Absent	Absent	No angina pectoris	Absent	Absent	Absent	Absent	64-70	20	158/112	3,750	
Absent	Absent	.....	Slight at rest	Intense at bases of both lungs	Intense	Intense	44-62	20	118/62 to 130/72	1,700 to 1,800	
Absent	Absent	.....	Absent on activity	Slight at base of left lung	Absent	Slight	38-44	20	122/80	1,800 to 1,900	
Absent	Absent	Frequent cardiac asthma attacks	Slight at rest	Moderate at bases of both lungs	Intense	Moderate	68-80	20	190/110	1,600 to 2,200	
Absent	Absent	No asthmatic* attacks for 20 days	Absent on activity	Absent	Absent	Absent	68-72	20	210/118	1,700 to 2,150	
Absent	Occasional	.....	Absent	Absent	Absent	Slight	60-80	20-24	110/72	2,000 to 2,400	
Absent	Absent	.....	Absent	Absent	Absent	Absent	60-70	18-20	120/80	2,300 to 2,700	
Absent	Absent	.....	Slight at rest	Absent	Slight	Moderate	60-80	20-24	134/80	1,750 to 1,850	
Absent	Absent	.....	Absent on activity	Absent	Absent	Slight	45-50	20-24	118/84	1,900 to 2,050	
Intense	Absent	Frequent severe asthmatic attacks	Absent	Moderate râles and rhonchi	Absent	Intense	84-100	20	104/80 to 120/80	1,900 to 2,400	
Slight to absent	Absent	Two slight attacks of wheezing	Absent	Râles absent; rhonchi present	Absent	Slight	68-80	20	118/84	2,750 to 3,100	

of the attack.  
several days later.

Approximately three and a half months after operation the patient was given work in the hospital in order to keep him under observation and to follow the course of his convalescence. His position demanded the transportation of bottles and medicines from one part of the hospital to another and kept him on his feet for approximately eight hours a day. He worked six and one-half full days a week and continued at this work for two weeks without complaint and without showing any evidence of circulatory insufficiency. There was no dyspnea, orthopnea, cyanosis or edema, and the lungs remained clear. He was later engaged as a helper in the research laboratory. At the time of writing he had been occupied in this capacity, working eight hours daily, for two months.

Six months after operation, with normal activity and work, he continued to maintain good health and showed no evidence of congestive failure. He had no complaints except for a few symptoms referable to the gastro-intestinal tract. There had been no attacks of angina pectoris, and palpitation appeared only follow-

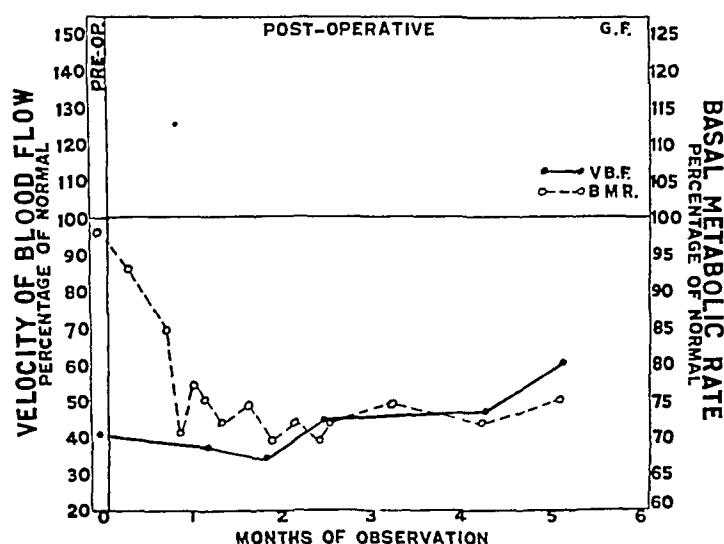


Chart 10 (case 11, or case 3 of previous communication).—The relation between the velocity of blood flow and the basal metabolic rate.

ing excessive effort. On May 16, 1933, five months after operation, he performed an exercise test without any evidence of dyspnea. He was able to walk a mile or more without dyspnea, and he could continue were it not for the sense of fatigue in his legs. He stated that he actually felt better after a given amount of exercise and for this reason took long walks regularly. The vital capacity increased after operation and continued at a level of approximately 500 cc. higher than it was prior to operation; the last readings varied from 2,900 to 3,200 cc.

The patient had a somewhat yellowish pallor, and the skin, particularly of the soles and palms, had become dry. The growth of hair had been noticeably retarded, shaving being necessary once a week as compared to once a day before operation. His hair had become coarser and somewhat dry. These signs and symptoms, however, had shown no progression in the last two months. His mind remained perfectly clear, and he was more than usually alert. The basal metabolism had continued low, and the velocity of blood flow remained slow. There had been no appreciable change in the red cell count and the hemoglobin since operation. The

slight secondary anemia present before operation, with a red cell count of 4,330,000 and a hemoglobin of 75 per cent (Sahli), had shown little change. Six months after operation, the red cell count was 4,220,000, and the hemoglobin was 70 per cent. Successive electrocardiograms showed no change.

*Comment.*—This patient with rheumatic heart disease, angina pectoris and congestive failure of three years' duration showed immediate improvement corresponding to the fall in the metabolic rate. At the time of writing he showed no evidence of congestive failure and at no time had he had dyspnea, palpitation, pain in the chest or edema in spite of the fact that he had been working eight hours a day during the preceding three months. His strength had increased, and his capacity to perform work was greater than at any time during the preceding three years. In spite of the permanent lowering of the metabolic rate and the development of mild unprogressive symptoms of myxedema, he remained mentally clear, was unusually alert and was capable of concentration in a highly satisfactory manner.

A summary of the important clinical findings before and after operation in the 10 patients of this series is given in table 3.

#### COMMENT

Two pitfalls in accurately evaluating a clinical therapeutic measure consist in the favorable effect of suggestion and spontaneous improvement due to changes in the natural history of the condition. Throughout this investigation we have tried to reduce such errors to a minimum. The patients were separated after operation so far as possible, and particular care was exercised to avoid leading questions. Only subjects who we felt could be relied on for intelligent reports of their subjective sensations were studied. The disappearance of orthopnea and the changes in the other objective signs of congestive failure have been particularly noted, and as many quantitative measurements as feasible have been made. To make it improbable that spontaneous changes could account for the improvement in any instance, only patients whose clinical course had remained practically unchanged or steadily progressive for many months or years were chosen. They had all received medical evaluation of their condition from time to time before coming to this hospital, and previous observations in other institutions and in this hospital were carefully studied. The beneficial effect of continued rest in bed during the preoperative study and postoperative convalescence could be safely discounted in the evaluation of the efficacy of total ablation, for all of the patients had previously had much longer periods of rest with adequate medical treatment without showing significant improvement. The medical treatment of all the patients was the same after operation as before it.



THE EFFECT OF TOTAL ABLATION OF THE THYROID  
ON ANGINA PECTORIS

The effect of total ablation of the thyroid on angina pectoris was observed in 2 patients, W. B. and A. B. (cases 4 and 5). Definite beneficial effect after operation was noted in the patient in case 5, who had increasingly frequent attacks over a period of eighteen months. After admission to the hospital, but before operation, he was able to walk up several flights of stairs at the prevailing warm temperature of the hospital without distress. The walking of short distances on level ground in the cold outdoor, winter weather provoked attacks readily, however. We realized that the weather would be warm during his postoperative convalescence and that the absence of attacks following the operation could not be attributed to the effects of complete ablation. It was decided, therefore, to study his condition in an environment which could be accurately controlled and which could be reproduced at will any time of the year. A Barach oxygen chamber filled with room air was cooled to approximately 52 F. Before operation, the same measured amount of work under such standard conditions regularly precipitated attacks on four different days. After operation, under the same conditions, as much as six times the same amount of work was performed without attacks of angina pectoris, the exercise being finally terminated because of physical exhaustion. Careful clinical notes, determinations of the blood pressure and pulse rate and other measurements were made; these observations, as well as others, will be the subject of a forthcoming communication.

The effect of operation on angina pectoris in case 4 was more difficult to evaluate, for the incidence of the preoperative attacks had become somewhat irregular and infrequent with the onset of congestive failure. It is worthy of note, however, that the patient is now able to walk about with greater freedom; he does not suffer from dyspnea or palpitation, and he has no cardiac pain.

There are undoubtedly several types of angina pectoris, and further observations on the effect of total ablation are desirable. These are being made. The manner in which relief is afforded by removal of the thyroid gland probably involves several different, though related, mechanisms. The decreased amount of work performed by the heart, the decreased metabolism of the heart itself and the decreased sensitivity to epinephrine are some of the possible factors that are being studied.

THE EFFECT OF COMPLETE ABLATION OF THE THYROID ON THE  
SYMPTOMS OF CONGESTIVE FAILURE

The effect of complete ablation of the thyroid on the symptoms of congestive failure was studied in each patient except the one in case 5, who suffered only from angina pectoris. Symptoms of congestive failure had been present in this group from two to twenty-six years; signs

of congestive failure, from one to twenty-six years. The average duration of the symptoms of congestive failure was twelve years; of the signs of congestive failure, seven years. The patients in cases 1, 2, 3, 6, 8, 9 and 10 had practically no cardiac reserve after prolonged periods of adequate medical treatment with complete rest in bed, so that the ability to be up and about without symptoms or signs of congestive failure could be attributed confidently to the effects of operation. The signs of congestive failure present when the patients were admitted to this hospital were not conspicuous, for all the patients had been in other hospitals for from months to years immediately preceding entry with the exception of the patients in cases 6, 7 and 9, who had been confined in bed at home under excellent medical supervision.

These patients showed a similarity in response that was impressive. This similarity could not have been due to suggestion, for they were separated in private rooms after operation. Within from three to fourteen days after operation, each one voluntarily stated that he felt "smoothed out" or "ironed out," that the pounding of the heart had diminished or disappeared and that slight shifts of position in bed which hitherto had caused violent palpitation could be accomplished without distress. By the end of the third or fourth week the patients noticed that whereas sedatives had previously been necessary to induce sleep, they were now able to sleep soundly without medication. Subjects who formerly suffered from orthopnea found that they were more comfortable when sleeping on one or two pillows. All noticed that they were able to breathe much more easily by the end of the third post-operative week and were unaware of the action of the heart. The pre-operative craving for water disappeared. Many, particularly those who were underweight, noticed increased appetite. The diet was increased in such instances, with a gain in body weight, amounting to as much as 20 pounds (9 Kg.) in the patient in case 2, who had been emaciated. In no instance was overweight permitted. On getting out of bed, from slight to moderate exertion was performed without palpitation or dyspnea. In one instance this had been impossible for as long as twelve years before operation (case 9).

These conspicuous changes in symptomatology may have been influenced to some extent by unavoidable suggestion, but the independent descriptions by each patient conformed so closely to one another and corresponded so closely to the objective findings to be detailed that one cannot fail to be impressed.

#### THE EFFECT OF TOTAL ABLATION OF THE THYROID ON SIGNS OF CONGESTIVE FAILURE

Each of the patients with congestive failure had edema on getting out of bed for even a brief period of each day. Up to the time of writing, each subject had been up and about the ward without sub-

jective distress and without any evidence of pitting edema or other signs of congestive failure. Râles, which were present at the bases of the lungs previous to operation, had disappeared; engorgement of the liver had lessened, as evidenced by a diminution in the size and the absence of tenderness. The ventricular rates of the patients had become steadier and had inclined to a lower level. The heart sounds had become definitely less hyperactive, and the thrust of the cardiac impulse had diminished. Less digitalis was necessary to control the ventricular rate in the patients suffering from auricular fibrillation.

Lessening of the cyanosis was evident in practically all the patients, and was conspicuous in the 2 most cyanotic patients (cases 6 and 10). In case 6, the red cell count had decreased, whereas in case 10, erythrocytosis had persisted unchanged. The more natural color of the skin after operation is probably due to the lessened engorgement of the minute vessels of the skin.

#### CHANGES IN CLINICAL MEASUREMENTS AFTER TOTAL ABLATION

*The Basal Metabolic Rate.*—There has been a significant lowering in the basal metabolic rate of each patient which, in accord with the considerations which led up to this investigation, has been closely paralleled by the clinical improvement in the circulatory condition. The decrease in the metabolic rate and the concomitant clinical improvement have occurred at various times after operation. The patients have been unaware of the results of metabolic measurements, but they always experienced their most striking improvement at the time when we found the rate lowered. Had their improvement been due to suggestion, one would have expected such improvement to be related in time to the operation rather than to reduction in the basal metabolic rate.

*The Velocity of Blood Flow.*—This remained greatly slowed in all the patients with a prolonged circulation time before operation. The measurements of the blood flow afford insight into the underlying mechanism of clinical improvement. In previous studies of the velocity of blood flow in patients with cardiac disease, it was found that when clinical improvement occurred under the usual medical procedure, the metabolic rate presumably remaining unchanged, the improvement was attended by an increased speed of blood flow.<sup>31</sup> The persistent slowing of the blood flow following operation in the cases reported in this communication indicates that the fundamental state of the circulation has not been altered. In terms of the law of supply and demand, we may say that the supply of blood has not been increased, but that the demands have been reduced to such an extent that the reduced supply is now adequate to the needs of daily life under these new circumstances.

31. Blumgart and Weiss,<sup>3a,b</sup> Blumgart and Weiss,<sup>2g</sup> Blumgart and Weiss,<sup>5b</sup> Blumgart, Gargill and Gilligan.<sup>3d</sup> Weiss and Blumgart.<sup>5d, e</sup>

The fact that patients who were unable to move about in bed without dyspnea before operation were able to climb the equivalent of two or three flights of stairs without discomfort after operation indicates that these patients have acquired a "cardiac reserve." There are several possible mechanisms which might bring this about. One rational explanation follows from the fact that in 7 of our patients the velocity of blood flow after total ablation of the thyroid became even slower than it was before operation. This indicates that after total ablation of the thyroid the heart does not work as hard as it showed itself capable of working before operation. The difference between the actual work done by the heart at rest after operation and the amount of work which it can do if necessary may be termed the "cardiac reserve."

These considerations may be represented diagrammatically. The diagonal line in chart 11, labeled "no congestive failure," repre-

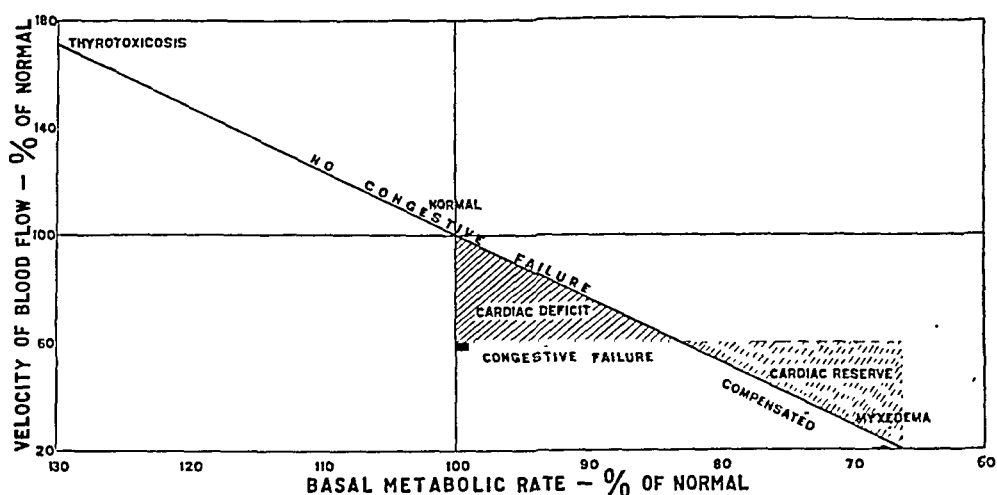


Chart 11.—Diagram showing the relationship between the velocity of blood flow and the basal metabolic rate in patients with no congestive failure and in patients with congestive failure. The line representing the relationship for patients with no congestive failure is based on previous findings.<sup>4</sup> The curve for patients with congestive failure is diagrammatically representative of the findings in a group of such patients before and after total ablation of the thyroid gland.

sents the relation between the velocity of blood flow and the basal metabolic rate in patients without congestive failure at various basal metabolic levels from thyrotoxicosis to myxedema. This line is plotted from actual measurements which were reported in a previous communication.<sup>4</sup>

The heavy horizontal line in chart 11, labeled "congestive failure," is diagrammatically representative of the relationship of the velocity of blood flow to the basal metabolic rate found in some patients with congestive failure. Such patients having 100 per cent of the normal basal metabolic rate and only 60 per cent of the normal velocity of blood flow

are decompensated persons. The degree of decompensation is represented on chart 11 by the discrepancy (read vertically) between the heavy line of "congestive failure" and the normal line of "no congestive failure." As the basal metabolic rate in such patients drops below normal following total ablation of the thyroid, the cardiac deficit becomes gradually less, the basal metabolic rate and velocity showing eventually the same relationship as in patients with similarly low basal metabolic rates and no congestive failure. At this point the slowed velocity of blood flow would be exactly sufficient for the metabolic demands of the patient at rest. As the basal metabolic rate becomes still lower, the velocity of blood flow would become proportionately slower. Seven of our patients have shown this slowing of velocity coincident with the decreasing basal metabolic rates. These patients possess, therefore, a "cardiac reserve" (chart 11), since the basal requirement placed on the heart is now less than the work that the heart is able to accomplish. The ability of the patients at the present time to undertake moderate exertion without palpitation, dyspnea and peripheral venous engorgement becomes explicable on the basis of these considerations.

*The Blood Pressure.*—There were no definite changes in the blood pressure following complete thyroidectomy, regardless of the level before operation.

*Electrocardiographic Changes.*—Changes were present in 7 patients within a few weeks after the initial fall in the metabolic rate. In 6 there was a decrease in the voltage of the Q R S complex, and in 4 a flattening of the T waves in one or more leads. The effect on premature contractions of the heart will be discussed later.

*The Vital Capacity of the Lungs.*—There was a decided increase in the vital capacity of the lungs in some patients, though not in all. The patients with no increase in vital capacity experienced as striking improvement in their respiratory symptoms as the others. In patients with congestive failure clinical improvement is practically always attended by an increased vital capacity of the lungs.<sup>32</sup> In a previous study of patients with myxedema, we observed, however, that the vital capacity of the lungs was abnormally low in spite of the absence of signs or symptoms of congestive failure.<sup>4</sup> Our observations in the present investigation are evidently a resultant of two opposing factors: (1) improvement in congestive failure tending to increase the vital capacity of the lungs, and (2) the development of the low metabolic rate of myxedema which tends to lower the vital capacity of the lungs.

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32. Drinker, C. K.; Peabody, F. W., and Blumgart, H. L.: The Effect of Pulmonary Congestion on the Ventilation of the Lungs, *J. Exper. Med.* **35**:77, 1922. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration: IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch. Int. Med.* **20**:443 (Sept.) 1917.

## EXERCISE TOLERANCE TESTS

By means of exercise tests standardized for each of the 9 patients with congestive failure, it was possible to demonstrate an increased ability to perform light work following ablation of the thyroid. The exercise consisted in repeatedly mounting a staircase of 2 steps, the process being repeated until the patient was forced to stop because of fatigue and dyspnea, or until the patient had performed the amount of work specified in the standards of Master and Oppenheimer.<sup>29</sup> For the individual patients this work ranged between 2,700 and 3,600 foot pounds and required from twenty-one to twenty-seven trips over the staircase for its performance. Persons with normal cardiovascular systems can perform this small amount of work readily and without discomfort. On completion of the exercise the pulse and blood pressure will show a sharp rise followed by a gradual return to the previous resting level in two minutes.

Before operation three of the patients were unable to complete the work prescribed for them, whereas in 2 others the test taxed their endurance to the limit. Two of the remaining patients required more than the ninety seconds usually needed to complete the exercise. In 4 of the patients the blood pressure showed a definite and, at times, striking fall on the completion of the test, and in 3 others the exercise failed to cause any significant rise in the blood pressure until the patients had rested for from thirty to ninety seconds. Four of these patients were near collapse on completion of this small amount of work. These patients showed pallor, perspiration, a weak and thready pulse, anxiety and marked dyspnea, all of which gradually disappeared after a few minutes of rest, leaving them greatly fatigued. In every case it required from four to eight minutes for the pulse and blood pressure to return to the resting level. The patient in case 6, who had well marked mitral stenosis, showed intense cyanosis immediately following the exercise.

Following operation all of the patients showed definite improvement in the facility with which they performed the test. In order to avoid so far as possible the factor of improved muscular tone as a result of increased activity, the test was first repeated within a few days after the patient was allowed out of bed. In most instances this first repetition of the test was performed when the basal metabolic rate had shown only a moderate drop and before the maximum improvement could be expected. Nevertheless, even at this early date it was found that many patients had to be restrained to prevent them from finishing the exercise in less time than they had previously required. All of the patients noticed less fatigue and dyspnea, and several volunteered the information that exertion caused "less pounding" and that they "finished stronger."

As the metabolic rate dropped further it became apparent that the patients were able to perform the exercise with increasing ease and with less discomfort, dyspnea and fatigue. The diminution in subjective discomfort was especially striking. The five patients whose endurance had been taxed to the utmost by the test were able to do more work without embarrassment. The actual increase in work varied with the patient and with the length of time during which the basal metabolism was maintained at a low level. There was in general a slight decrease in the length of time taken for the pulse and blood pressure to return to the resting level. In only 1 instance did the blood pressure fail to show a sharp rise following the exercise, and in this person the post-operative test was performed within two weeks after the basal metabolism began to fall and within a few days after the patient had been up and around for the first time since the operation. In this person, the drop in the blood pressure which occurred was not so great as before the operation. On the basis of our experience with the other patients, it is to be expected that this patient will show further improvement in her response to exercise.

Case 1 best illustrates the changes in results of the exercise tolerance test following thyroidectomy. Three days before operation this patient performed 3,640 foot pounds of work. At that time he weighed 140 pounds (63.5 Kg.), and twenty-six trips were required to perform the work. He was unable to perform the exercise in less than two minutes. At the completion of this work he had to be helped to his chair. He was pale, perspired freely and was completely exhausted. The blood pressure, which was 104 systolic and 58 diastolic before the exercise, fell to 80 systolic and 40 diastolic. Two minutes later it reached its maximum height of 120 systolic and 56 diastolic and did not fall to the resting level until eight minutes after completion of the exercise. The pulse became thready; it rose from 88 to 136 and required four and one-half minutes to return to normal. There was marked dyspnea which did not subside for about eight minutes.

The test was repeated forty-eight days after operation. At this time the patient weighed 163 pounds (74 Kg.), and only twenty-three trips were required to perform 3,750 foot pounds of work. Throughout the exercise he had to be held back so that he would not finish the work in less than one and a half minutes. When the patient was at rest the blood pressure was 112 systolic and 70 diastolic. Following exercise it rose sharply to 160 systolic and 62 diastolic; it returned to normal in five and one-half minutes. The pulse rate rose from 92 to 140; it returned to normal in three minutes. There was very slight dyspnea for only three minutes. At the completion of the exercise the patient

experienced only slight fatigue and could have continued. On the following day he performed thirty-five trips (5,670 foot pounds) and stopped because the muscles of the thighs felt fatigued, and he began to experience slight shortness of breath. His blood pressure and pulse showed essentially the same curve as on the previous day.

THE EFFECT OF TOTAL ABLATION OF THE THYROID ON HEMOPTYSIS,  
HEART FAILURE PAIN AND OTHER ASSOCIATED SYMPTOMS  
AND SIGNS OF CONGESTIVE FAILURE

The effect of total ablation of the thyroid on hemoptysis, heart failure pain and other associated symptoms and signs of congestive failure have been striking. In patient E. W. (case 1), hemoptysis had occurred at frequent intervals for seven years. During the previous eighteen months hemoptysis had occurred as often as every day for weeks with occasional periods of freedom, the longest being two weeks. During the week immediately before operation hemoptysis occurred daily and inclined us somewhat against operation. Shortly after operation slight hemoptysis occurred once; there has been no recurrence in spite of the fact that the patient had been up and about the hospital the entire day for several weeks and in spite of his recent return home, where he has been active though not yet at work. The patients in cases 2, 6 and 8 likewise had suffered from hemoptysis before entry, though so irregularly that the absence of hemoptysis over the comparatively short postoperative period cannot be considered significant.

One of the most striking changes in patients with congestive failure has been the disappearance of pain in the chest. The patient in case 1 had suffered for five years from transient pains and aches referable to the precordium, sternum, neck, shoulders and arms. The patient in case 2 had pain in the chest anteriorly; the one in case 3 had suffered from a sense of thoracic compression; the one in case 6 had noted localized precordial pain; the one in case 8 had precordial pain which radiated to the left shoulder, and the patient in case 9 had been troubled by pain in the region of the left nipple whenever she had exerted herself during the previous three years. These sensations had been so constant that the patients had learned to minimize and practically ignore them. Only on the disappearance of the pains did some of the patients realize how constant and discomforting the symptoms had been. In all of these persons the symptoms disappeared coincident with a lowering of the basal metabolic rate; they did not recur even after an amount of exercise which had been impossible for many years.

*The disappearance of premature contractions* of the chambers of the heart has been interesting to note in cases 3, 5 and 8. In case 5, ventricular premature impulses which were present before operation were not observed after operation. In cases 3 and 8, the premature auricular



impulses which were present before operation disappeared after operation, when the basal metabolic rate was low. In case 3, the premature beats recurred when thyroid medication was given and disappeared again after omission of the drug, when the metabolic rate returned to its previously low level. These observations make it conceivable that attacks of paroxysmal auricular tachycardia, otherwise uncontrollable, may be favorably affected by total ablation of the thyroid.

#### THE EFFECT OF TOTAL ABLATION OF THE THYROID ON PAROXYSMAL DYSPNEA

The therapeutic effect of total ablation of the thyroid on attacks of paroxysmal dyspnea has been less encouraging than in the other types of cardiovascular disease. The patient in case 4 had previously suffered from such attacks and felt entirely well after operation. The incidence of these attacks before operation was too irregular to warrant placing much significance on their absence during the relatively short post-operative period. The patient in case 7, on the other hand, had suffered from repeated attacks for many weeks before operation, and we were encouraged by the absence of attacks after operation and the disappearance, at the same time, of signs and symptoms of mild congestive failure. According to the concept that paroxysmal dyspnea is due to a relative diminution in the output of the left ventricle,<sup>33</sup> we hoped that the decreased work of the heart at a low metabolic rate might obviate acute weakening of the left chambers of the heart. It is possible, however, that acute exacerbations of extremely high blood pressure, such as occurred in this case, may place too great a burden on the left ventricle. We cannot be certain of this mechanism, however, for while blood pressure readings were taken within a few minutes of the onset of the attack and exceeded the limit of the top of the mercury manometer column, i. e., 300 mm., we do not know whether the elevation in blood pressure actually preceded the attack. It is possible that after thyroidectomy a disproportionate output of the two ventricles may also exist at a lower level and may amount to less than that at the previous normal metabolic level. In any event, further experience is necessary in order to evaluate the benefit that may be derived from thyroidectomy in this condition, and more prolonged rest in bed after operation probably is indicated. The disappearance of all signs of congestive failure and the absence of attacks for three weeks make it seem possible that the treatment may be attended with greater success in patients afflicted less severely and with less elevated blood pressure.

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33. Weiss, S., and Robb, G. P.: The Mechanism and Treatment of the Paroxysmal Dyspnea and Asthma Associated with Heart Disease, *New England J. Med.* **205**:1172, 1931; The Treatment of Cardiac Asthma, *M. Clin. North America* **16**:961, 1933.

THE DEVELOPMENT OF THE SIGNS AND SYMPTOMS OF CLINICAL  
MYXEDEMA AFTER TOTAL ABLATION OF THE THYROID

The development of the signs and symptoms of clinical myxedema has been carefully observed. With the reduction in the basal metabolic rate all patients have felt calmer and less nervous. The uniformity with which patients have used the terms "smoothed out" and "ironed out" has been interesting. The heart rate has tended to be lower; the respiratory rate has become slightly slower and, in the patients subject to fluctuations, much steadier. The temperature has not changed perceptibly. Within from four to six weeks the skin has become somewhat paler, has acquired a slightly yellowish tint and has become somewhat dry. After the metabolic rate decreased to minus 30 per cent, some patients complained of coldness of the feet and required more blankets. Several patients who formerly shaved once daily required a shave only every several days; the patient in case 11 (case 3 of the previous communication) now shaves but once a week.

Each of us has been impressed with the fact that in every patient, instead of the mental lethargy of myxedema, unusual brightness and alertness have been present during the months that they have been studied. Each of the patients has spontaneously commented on this change. This is probably due to the fact that these patients compare their postoperative mental condition with the grogginess of circulatory failure, and that mental lethargy is a manifestation of more advanced myxedema.

Measurements of the heart from roentgenograms taken at a distance of 7 feet have not shown any postoperative changes to date. Particular attention has been devoted to the appearance of evidence of the signs or symptoms of the so-called myxedema heart.<sup>34</sup> Assmann,<sup>35</sup> Fahr<sup>36</sup> and others have described a form of myocardial failure characteristic of myxedema which is alleviated only by thyroid therapy. On the other hand, Means, White and Krantz,<sup>37</sup> in a study of 48 patients with myxedema, encountered but 1 such case. In 162 cases Willius and Haines<sup>38</sup> found no evidence of heart failure or of organic cardiovascular disease that could be attributed to the myxedema. Christian<sup>39</sup> similarly stated that he had never observed the condition.

34. Zondek, H.: *Das Myxödemherz*, München. med. Wchnschr. **65**:1180, 1918.

35. Assmann, H.: *Das Myxödemherz*, München. med. Wchnschr. **66**:9, 1919.

36. Fahr, George: *Myxedema Heart*, J. A. M. A. **84**:345 (Jan. 31) 1925.

37. Means, J. H.; White, P. D., and Krantz, C. I.: *Observations on the Heart in Myxedema*, Boston M. & S. J. **195**:455, 1926.

38. Willius, F. A., and Haines, S. F.: *The Status of the Heart in Myxedema*, Am. Heart J. **1**:67, 1925.

39. Christian, H. A.: *Myocardial Disturbances Due to Abnormal Thyroid Function and Their Management*, Pennsylvania M. J. **32**:70, 1928.

More numerous examples of the opposite course of events are available, namely, thyroid therapy precipitating circulatory insufficiency rather than alleviating it. Swan<sup>40</sup> has reported the case of a patient with myxedema in whom fibrillation of the auricles appeared whenever thyroid substance was administered, the heart action returning to normal whenever the drug was discontinued. Read<sup>41</sup> and Means, White and Krantz<sup>37</sup> have reported cases in which the administration of thyroid substance caused attacks of angina pectoris. Sturgis and Whiting<sup>42</sup> and Pratt and Morton<sup>43</sup> observed patients in whom, on each attempt to give thyroid gland, the signs of congestive failure appeared. Christian<sup>44</sup> has laid particular emphasis on the danger of increasing the heart action of certain myxedematous patients by thyroid medication.

In a recent review of hypothyroid heart disease, Means described the enlarged heart shadow occurring in almost all the cases studied at the Massachusetts General Hospital and shrinkage in the transverse diameter following thyroid therapy.<sup>45</sup> Should any untoward effects of myxedema on the heart become manifest in our cases, some elevation of the metabolic rate by thyroid substance may be advisable.

#### MEDICAL MANAGEMENT OF THE OPERATIVE COURSE

All of the patients were observed for periods ranging from two weeks to two months before operation. While we were studying the extent of their cardiac reserve and making an appraisal of their general medical condition, the physical condition was improved to the fullest possible extent in order to minimize the risk of operation.

Several days before operation the patients received a therapeutic dose of morphine sulphate so that we could be certain that the drug caused its characteristic sedative effect. In several instances the drug had a stimulating effect, causing insomnia, excitement and other conditions; barbituric acid derivatives were employed in such subjects immediately before operation.

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40. Swan, J. M.: A Case of Auricular Fibrillation Occurring During the Administration of Thyroid Substance, *Ann. Clin. Med.* **3**:311, 1924.

41. Read, J. M.: Treatment of the Cardiac Disturbances Due to Thyroid Disease, *J. A. M. A.* **89**:493 (Aug. 13) 1927.

42. Sturgis, C. C., and Whiting, W. B.: The Treatment and Prognosis in Myxedema, *J. A. M. A.* **85**:2013 (Dec. 26) 1925. Sturgis, C. C.: Angina Pectoris as a Complication in Myxedema and Exophthalmic Goiter, *Boston M. & S. J.* **195**:351, 1926.

43. Pratt, G. P., and Morton, H. B.: Management of the Circulation in Myxedema, *Am. J. M. Sc.* **173**:274, 1927.

44. Christian, H. A.: The Heart and Its Management in Myxedema, *Rhode Island M. J.* **8**:109, 1925.

45. Means, J. H.: Hypothyroid Heart Disease, *New England J. Med.* **208**:541, 1933. Lerman, J.; Clark, R. J., and Means, J. H.: The Heart in Myxedema: Electrocardiograms and Roentgen-Ray Measurements Before and After Therapy, *Ann. Int. Med.* **6**:1251, 1933.

Immediately before and throughout the operation the state of the cardiovascular system was carefully observed, and occasionally, when indicated, additional digitalis was given. Although various general anesthetics were used at the beginning of this investigation, we have found gas-oxygen anesthesia the most satisfactory one at our disposal. In 2 patients a small amount of ether was employed as a supplementary anesthetic.

Following operation, sedatives were again administered when necessary. Edema was present in some of the patients, and in these cases hypodermoclyses were not given. From 500 to 1,000 cc. of physiologic solution of sodium chloride was given subcutaneously to other patients. For some patients who drank fluids shortly after the operation without discomfort or difficulty, parenteral administration of fluids was considered unnecessary.

We have not encountered serious parathyroid tetany. All of the patients were instructed to report to the nurse on duty, or to us, the onset of numbness, tingling, "queer sensations" and other symptoms, and were also questioned several times daily. During the first week of the postoperative course, repeated measurements of the calcium content of the blood were made, and tests were carried out at intervals of from three to six hours for Chvostek's and Trousseau's signs. Such signs became evident in 2 patients. From 2 to 8 cc. of a 35 per cent solution of calcium chloride orally from four to six times a day, and 0.5 cc. of viosterol, 250 D, four times daily, have controlled the symptoms and signs. Decreasing amounts have been given without recurrence of the symptoms or signs, and it appears possible that medication may become unnecessary. A quart of milk was also included in the diet. Parathyroid extract-Collip was not employed except in 1 patient. A single dose was given by the nurse, according to our standing orders for the night when Chvostek's and Trousseau's signs became evident.

We have not administered compound solution of iodine to any of our patients before operation, for iodine does not lower the basal metabolic rate in patients with normal thyroids and has been described as activating quiescent adenomas.

The greatest danger in this operation, we believe, is injury to the recurrent laryngeal nerves.<sup>46</sup> Laryngoscopic examinations were made before, during and after the operations through the cooperation of Dr. Louis M. Freedman. Direct laryngoscopic examination was made after complete ablation of one-half the thyroid gland. Though it has

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46. Berlin, D. D., and Lahey, F. H.: Dissections of the Recurrent and Superior Laryngeal Nerves (The Relation of the Recurrent to the Inferior Thyroid Artery and the Relation of the Superior to Abductor Paralysis), Surg., Gynec. & Obst. **49**:102, 1929.

not been necessary thus far, we intend to terminate the operation at this stage should the recurrent laryngeal nerve be affected. The operation may be completed at a later date if the nerve regains its function.

Immediately after operation one of the patients showed a recurrence of râles and rhonchi over the dependent portions of both lungs. In some patients there was a postoperative reaction with a temperature of 103 F. and corresponding elevations in the cardiac and respiratory rates. Discomfort was readily controlled by sedatives, and the condition of none of the 10 patients warranted grave concern. Approximately half of the patients of this series showed no appreciable postoperative rise in the temperature or the pulse and respiratory rates.

The degree of local discomfort varied considerably; some patients talked immediately after operation and took solid food and liquids without discomfort, while a few complained of local soreness in the region of the wound and had pain on swallowing during the first few days, which gradually disappeared by the fifth or sixth postoperative day. The surgical details of the operative procedure and the precautions to be observed have been described in a previous communication.<sup>47</sup>

#### OPERATIVE MORTALITY

Besides the 10 cases recorded in this communication, 1 postoperative death occurred in the present series thirty-six hours after thyroidectomy, owing to pulmonary complications. This patient was 62 years of age and had suffered from congestive failure for many years. The diagnosis was generalized arteriosclerosis and advanced aortic stenosis and insufficiency. The patient showed no stridor after operation, but was troubled by the accumulation of considerable mucus. Bronchopneumonia resulted and was evidently caused by a combination of excessive secretion of mucus and injury of the recurrent laryngeal nerve, which made it difficult for the patient to cough up the accumulated mucus. This patient was the only one of the series on whom tracheotomy was performed. In retrospect, we are inclined to believe that tracheotomy should be employed early, in accord with the experience of Crile.<sup>48</sup> Including the patients in the cases reported in the previous communication, 16 patients have been operated on with 2 postoperative deaths. The first death was also due to postoperative pulmonary complications, with mediastinitis possibly as a result of the opening up of the fascial planes of the

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47. Berlin, D. D.: The Therapeutic Effect of Thyroidectomy on Congestive Heart Failure and Angina Pectoris in Patients with No Clinical or Pathological Evidence of Thyroid Toxicity: II. Operative Technic, *Am. J. Surg.* **21**:173 (Aug.) 1933.

48. Crile, George, and others: *Diagnosis and Treatment of Diseases of the Thyroid Gland*, Philadelphia, W. B. Saunders Company, 1932.

lower part of the neck. In subsequent operations the lower portion of the neck has been exposed as little as possible, and this complication has not been encountered.

When one considers the poor physical condition of our subjects and their lack of cardiac reserve, the mortality of the operation to date has been fortunately low. Complications which proved fatal in these cases might have been withstood by patients in better condition. One patient who decided not to have the operation died three days after leaving the hospital, and in 2 others hemiplegia developed a few days before the date planned for operation. With increasing experience, we believe that the mortality rate of this operation can, nevertheless, be further reduced.

#### THE ADVANTAGES AND DISADVANTAGES OF TOTAL ABLATION OF THE THYROID

Total ablation of the thyroid was performed on all of the patients in this series. The reasons for so doing have been discussed in a previous communication.<sup>1</sup> Subsequent experience has reenforced our belief that this is the operation of choice, for in each of the 11 patients operated on, a conspicuous lowering of the basal metabolic rate has, up to the time of writing, been maintained. In contrast to this, extensive subtotal removal of the thyroid, performed on 2 patients with congestive failure, resulted in only temporary lowering of the basal metabolic rate,<sup>1</sup> and both patients have relapsed to their preoperative clinical condition. In 1 patient (case 2 of the preceding series) an attempt was made subsequently to remove the remaining fragments of thyroid tissue, without success. Irradiation therapy in this case, as well as in others to be reported, has likewise been attended with uncertain results. Subtotal thyroidectomy may at times be attended by improvement, but the uncertainty of beneficial results and the further uncertainty of being able to remove the residual thyroid tissue at a subsequent operation contraindicate this procedure.

In contrast to the clinical course of the 2 patients on whom subtotal thyroidectomy was performed has been the clinical course of patient G. F., who was the first person on whom total ablation of the normal thyroid was performed, six months ago.<sup>1</sup> This patient had been confined to bed for more than two years because of congestive failure. During that time he continually suffered from dyspnea, orthopnea and transient attacks of pain in the chest. Even turning over in bed or combing his hair caused violent palpitation. Râles at the bases of the lungs, pitting edema of the legs and hepatic enlargement were constantly present.

The results of ablation of the thyroid four weeks after operation have already been reported.<sup>1</sup> At that time the basal metabolic rate had reached a level of minus 28 per cent, and coincident with this there was

striking improvement in the clinical condition. The preoperative thirst, palpitation, dyspnea, orthopnea, cyanosis, edema and hepatic tenderness disappeared, and he became free from pain in the chest.

Six months have elapsed since the operation was performed, and during this time the low metabolic rate and the clinical improvement have been maintained. During the past three months the patient has been working forty-eight hours a week and has been on his feet practically the entire day. With the increase in activity he has gradually gained muscular strength, so that he is able to walk as far as a mile without dyspnea or fatigue. At no time has he noticed cough or edema. He sleeps soundly with only one pillow.

Signs of mild hypothyroidism have developed. There is a yellowish tinge to the skin. The patient now shaves but once a week, whereas formerly this was a daily necessity. His feet feel cold, so that he wears woolen socks in May. He shows none of the mental slowing, however, which is usually associated with myxedema.

From a state of uncomfortable chronic invalidism the patient has been restored not only to moderate activity without discomfort, but to a condition of occupational usefulness.

This communication presents only the early results following operation. The patient in case 5 was unable to work because of angina pectoris, and the other patients were completely incapacitated and forced to remain in bed practically all the time. To date, we may say that months of effective life have been added to the lives of these patients. In effect, we seem to have extrapolated backward on the life history curve of their disease. In patients with rheumatic valvular disease, the obstruction or insufficiency of the valves has not been affected, nor has the level of the blood pressure been altered in patients with hypertension. The underlying mechanism of paroxysmal dyspnea does not seem to be completely obviated. Appraisal of the ultimate value of this procedure must, therefore, await continued study of these patients and other patients, who we hope will be observed by other investigators. The broad general considerations of the supply of blood and metabolic demand which underlie this investigation may be applicable to other fields. One of our patients suffered from Paget's disease, and we are observing his condition carefully. Patients suffering from other metabolic disorders, such as diabetes mellitus, may conceivably benefit from a reduced metabolism. The improvement shown by 1 of our patients with bronchial asthma is likewise suggestive. Whether a reduced metabolic rate will affect chronic infections, such as tuberculosis, favorably or adversely cannot be foretold with certainty. These phases of the problem are being studied.

It is hoped that ultimately operation will be unnecessary to produce a low metabolic rate. Many studies have been made on antithyroidal substances, and comparatively recent reports give hope that the administration of such substances may cause lowering of the metabolic rate.<sup>49</sup>

Because of the uncertainty as to the ultimate duration of the beneficial results, we feel that this operation should be undertaken at the present time only on patients with congestive failure or angina pectoris in whom the operative risk is fair and in whom all other medical procedures have been employed without the desired therapeutic results. Patients with active coronary disease, active infection, repeated pulmonary infarctions, vascular accidents or rapidly progressive syphilitic cardiovascular disease are probably unfavorable subjects.

SUBSEQUENT NOTE: Since this paper has been in press, each patient has shown further improvement. Some patients who at the time of writing were up and about without distress are now able to walk several miles daily. The basal metabolic rates have remained low and the velocity of blood flow, slow.

#### SUMMARY AND CONCLUSIONS

1. The early therapeutic results following total ablation of the thyroid in 10 patients with congestive heart failure or angina pectoris are reported.

2. The subsequent clinical course of the first patient who was treated by this procedure, six months ago, and whose case was described in a previous communication is given.

3. The clinical observations which provided the rationale for this procedure are given, and the historical background is reviewed.

4. Attacks of angina pectoris, which were present in 2 patients before operation, have not recurred since complete thyroidectomy. In 1 of these patients, before operation the same measured amount of work under standard conditions regularly precipitated attacks. After operation, under the same conditions, as much as six times the same amount of work was performed without attacks of angina pectoris, the exercise being finally terminated because of physical exhaustion.

5. Seven of the 9 patients with congestive failure had practically no cardiac reserve after prolonged periods of adequate medical treatment

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49. Anselmino, K. J., and Hoffmann, F.: Darstellung, Eigenschaften und Vorkommen einer antithyreoiden Schutzsubstanz aus Blut und Geweben, *Klin. Wchnschr.* **12**:99, 1933. Romeis, B.: Untersuchungen über die Wirkung des Thyroxins: III. Ueber die Zerstörung der spezifischen Wirkung des Thyroxins durch die Einwirkung von Blut in vivo und in vitro, *Biochem. Ztschr.* **141**:500, 1923.



with complete rest in bed, so that the ability to be up and about without symptoms or signs of congestive failure could be attributed confidently to the effects of operation.

6. During the period of observation of three to six months that have elapsed since operation, all of the patients have shown conspicuous improvement. They have been able to undertake from slight to considerable exertion without the development of palpitation, dyspnea or any signs of congestive failure. The preoperative craving for water has disappeared.

7. The basal metabolic rate of each patient has shown a significant and persistent lowering which has paralleled the most striking improvement.

8. The velocity of blood flow has become slower in 7 patients, indicating that the heart is required to do less work under the new post-operative condition than it was able to accomplish when the metabolic rate was normal. These patients may therefore be regarded as being in possession of a definite "cardiac reserve."

9. The vital capacity of the lungs showed a decided increase in some patients, though not in all. The significance of these findings is discussed.

10. By means of exercise tests standardized for each of the 9 persons with congestive failure, an increased ability to perform light work after operation has been demonstrated.

11. Frequently recurring hemoptysis and pain in the chest have disappeared following operation.

12. One patient who suffered from paroxysmal dyspnea showed improvement for three weeks following operation. On the twenty-second day he suffered from an attack of acute pulmonary edema during which he died. Further experience is necessary to evaluate the possible benefit to be derived from thyroidectomy in this condition, and operation should be undertaken in this type of cardiovascular disease with extreme caution.

13. Following operation patients have had slight dryness of the skin, increased sensitivity to cold, slow growth of hair and a lower heart rate. Thyroid substance has not been given except for short periods to 2 patients; in the others, it has not been indicated thus far.

14. The medical management of the operative course is described.

15. In 1 patient with congestive failure who had suffered from continuous attacks of bronchial asthma since childhood, no severe attacks have occurred since operation. The possible beneficial effects of the procedure in other conditions are discussed.

16. Because of the inevitable uncertainty as to the ultimate duration of the beneficial results, we feel that this operation should be undertaken at the present time only on patients with congestive failure or angina pectoris, in whom the operative risk is fair and in whom all other medical procedures have been employed without the desired therapeutic results. Patients with active coronary disease, active infection, vascular accidents, repeated pulmonary infarctions or rapidly progressive syphilitic cardiovascular disease are probably unfavorable subjects.

# CLINICAL STUDIES OF RESPIRATION

## II. INFLUENCE OF DETERMINATION OF BASAL METABOLISM ON RESPIRATORY MOVEMENTS IN MAN, AND EFFECT OF THESE ALTERATIONS ON CALCULATED BASAL METABOLIC RATE

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In a preceding paper,<sup>1</sup> a plethysmographic method was described for the study of the respiratory movements in man, and it was shown that in repose the expiratory position of the chest is usually, though not necessarily, almost constant, and that it may be altered by a change in the position of the body, by muscular activity or by speech.

The alteration that accompanied muscular activity appeared to be due to a psychic or reflex mechanism. In order to investigate the latter factors further, the influence of the determination of basal metabolism on the respirations was studied.

When the basal metabolic rate is determined, a face mask or a mouthpiece and nose-clip are used in connecting the subject's lungs to the spirometer. The application of this apparatus produces a psychic or reflex reaction in some subjects, and the respirations are materially altered. It was noted by Carpenter,<sup>2</sup> in comparing the different methods for the determination of gaseous exchange, that there was a distinct alteration of the respiratory movements in some subjects.

### METHOD

Thirty-four studies were made on three normal members of the laboratory staff and twenty patients from the hospital wards. A continuous record of the respiratory movements was obtained before, during and after the metabolic test.

With the patient in the postabsorptive state and quieted by a rest period of from thirty to forty-five minutes, the respirations were recorded for from fifteen to twenty minutes by the plethysmographic method. Then without interruption of the

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1. Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respiration: I. A Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities on the Expiratory Position of the Chest in Man, *Arch. Int. Med.* **52**:44 (July) 1933.

2. Carpenter, T. M.: A Comparison of Methods for Determining the Respiratory Exchange of Man, Washington, D. C., Carnegie Institution, 1915, pub. no. 216.

plethysmographic record the gaseous exchange was determined by the closed circuit method. The carbon dioxide was absorbed and weighed.

Each metabolic study was divided into two periods of six minutes each. The mouthpiece and nose-clip were not removed, but the expired air was diverted to other absorptive containers, and oxygen, when needed, was added to the spirometer.

The plethysmographic record was continued for from ten to thirty minutes after the metabolic study had been completed.

TABLE 1.—*Alterations in Respiratory Movements During Determination of Basal Metabolic Rates in Twenty-Three Persons*

Case	Diagnosis	Test No.	Change in Rate	Change in Amplitude	Change in Expiratory Position	Change in Ventilation	Rhythm	Change in Rhythm	Previous B.M.R.
1	Normal.....	1	0	Inc.	0	Inc.	Reg.	0	Yes
		2	0	Inc.	0	Inc.	Reg.	0	
2	Normal.....	1	0	Inc.	0	Inc.	Reg.	0	Yes
		2	0	Inc.	0	Inc.	Reg.	0	
3	Normal.....	1	Dec.	Inc.	Inc.	Inc.	Und.	Reg.	No
4	Psychoneurosis.....	1	0	Inc.	0	Inc.	Reg.	0	Yes
5	Psychoneurosis.....	1	0	Inc.	0	Inc.	Reg.	0	Yes
		2	0	Inc.	0	Inc.	Reg.	0	
6	Psychoneurosis.....	1	0	Inc.	0	Inc.	Reg.	0	Yes
		2	Inc.	Inc.	0	Inc.	Reg.	0	
7	Effort syndrome.....	1	0	0	Inc.	(?)	Und.	0	Yes
		2	0	0	Inc.	(?)	Und.	0	
8	Polycythemia.....	1	0	Inc.	0	Inc.	Und.	Reg.	Yes
		2	0	Inc.	0	Inc.	Und.	0	
		3	0	Inc.	0	Inc.	Reg.	0	
9	Hyperthyroidism.....	1	Dec.	Inc.	0	Inc.	Reg.	0	Yes
		2	Dec.	Inc.	0	Inc.	Reg.	0	
10	Hyperthyroidism.....	1	Inc.	Inc.	0	Inc.	Sig.	0	No
11	Hyperthyroidism.....	1	0	Inc.	0	Inc.	Reg.	0	No
12	Myxedema.....	1	0	Inc.	0	Inc.	Reg.	0	No
		2	0	Inc.	0	Inc.	Reg.	0	
13	Colloid goiter.....	1	0	Inc.	0	Inc.	Sig.	0	Yes
14	Pernicious anemia.....	1	0	Inc.	0	Inc.	Reg.	0	No
		2	0	Inc.	0	Inc.	Reg.	0	
15	Pernicious anemia.....	1	0	Inc.	0	Inc.	Und.	0	No
16	Pernicious anemia.....	1	0	Inc.	0	Inc.	Reg.	0	No
17	Pernicious anemia.....	1	0	Inc.	0	Inc.	Reg.	0	No
18	Diabetes (mild).....	1	Inc.	Inc.	Inc.	Inc.	Reg.	0	No
19	Rheumatic heart disease (decompensated)	1	0	Inc.	0	Inc.	Reg.	0	Yes
20	Myelogenous leukemia..	1	Dec.	Inc.	0	Inc.	Reg.	0	No
		2	Dec.	Inc.	0	Inc.	Reg.	0	
21	Enuresis.....	1	Dec.	Inc.	0	0	Reg.	0	No
22	Pregnancy.....	1	0	Inc.	0	Inc.	Und.	0	No
23	Pulmonary tuberculosis	1	0	Dec.	Inc.	Dec.	Reg.	0	Yes

and Inc. and Dec. and Inc.

No change is indicated by 0; an increase, Inc.; a decrease, Dec.; regular respiration, Reg.; undulatory respiration, Und., and sighing respiration, Sig.

#### INFLUENCE OF THE DETERMINATION OF THE BASAL METABOLISM ON THE RESPIRATORY MOVEMENTS

The respiratory movements were altered during the metabolic study in all the subjects. The results are given in table 1.

The respiratory rate was increased in three subjects. During a previous study there had been no change in rate in one of these subjects.

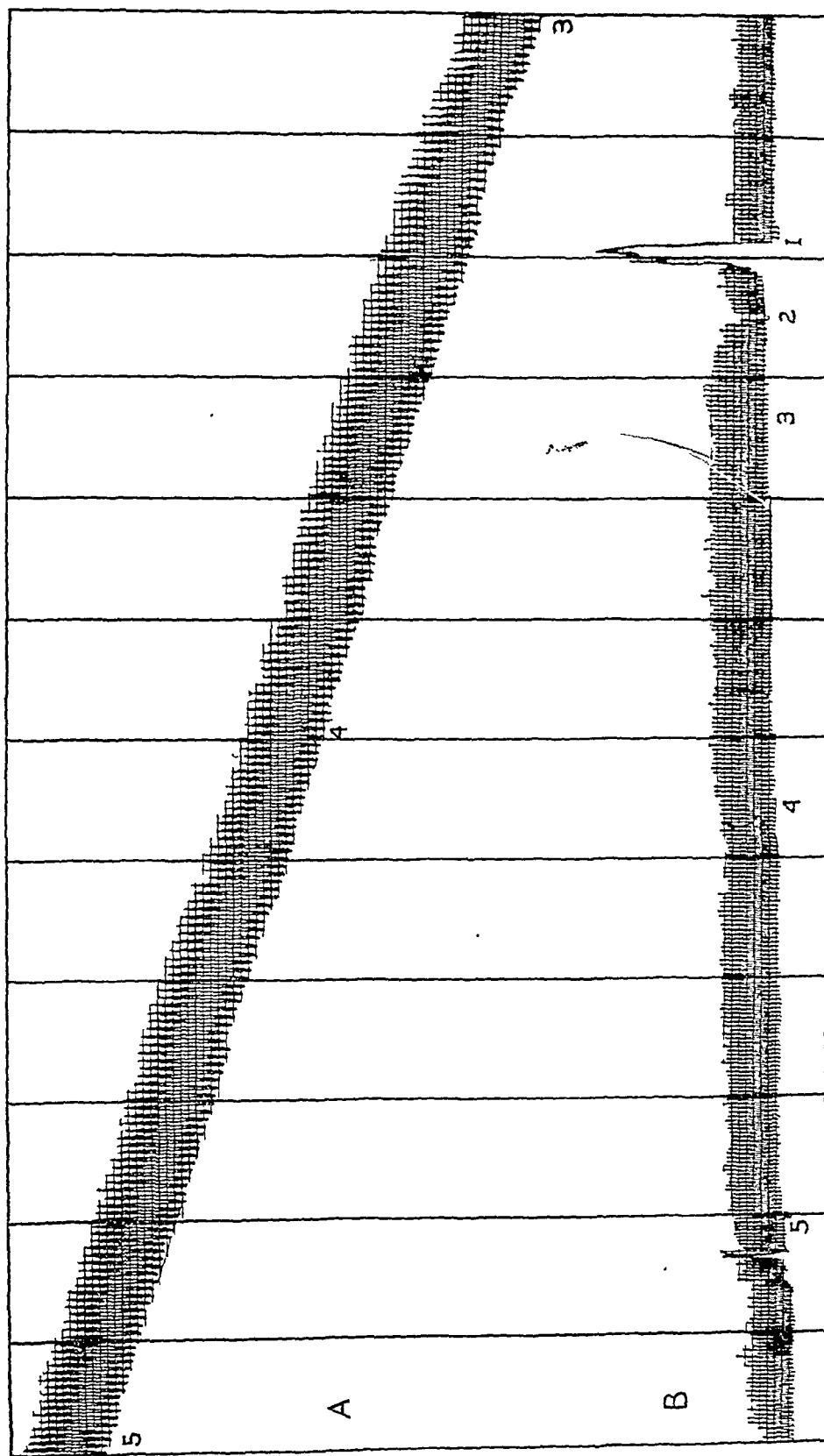


Chart 1.—Graph *A* is a spirographic, and graph *B*, a plethysmographic, record. The graphs are read from right to left, and the down stroke indicates expiration. At 1 the mouthpiece was inserted; at 2 the nose-clip was applied; at 3 the expired air was diverted to weighed absorptive containers; at 4 it was diverted to the second weighed absorptive containers, and at 5 the metabolic test was discontinued.

The rate was decreased in four subjects during six examinations. It was unchanged in seventeen subjects during twenty-five examinations.

The amplitude of the respiratory movements increased in twenty-one subjects during thirty-one of the thirty-four examinations. The two extremes of change in amplitude are shown in charts 1 and 2. The amplitude decreased slightly in subject 23 during the first period of study, and increased slightly during the second period. There was no change in amplitude in subject 7 during two examinations.

The rhythm was altered in two subjects during two examinations. Before the metabolic determinations were made, the respiratory movements in seven examinations of five subjects were undulatory. This

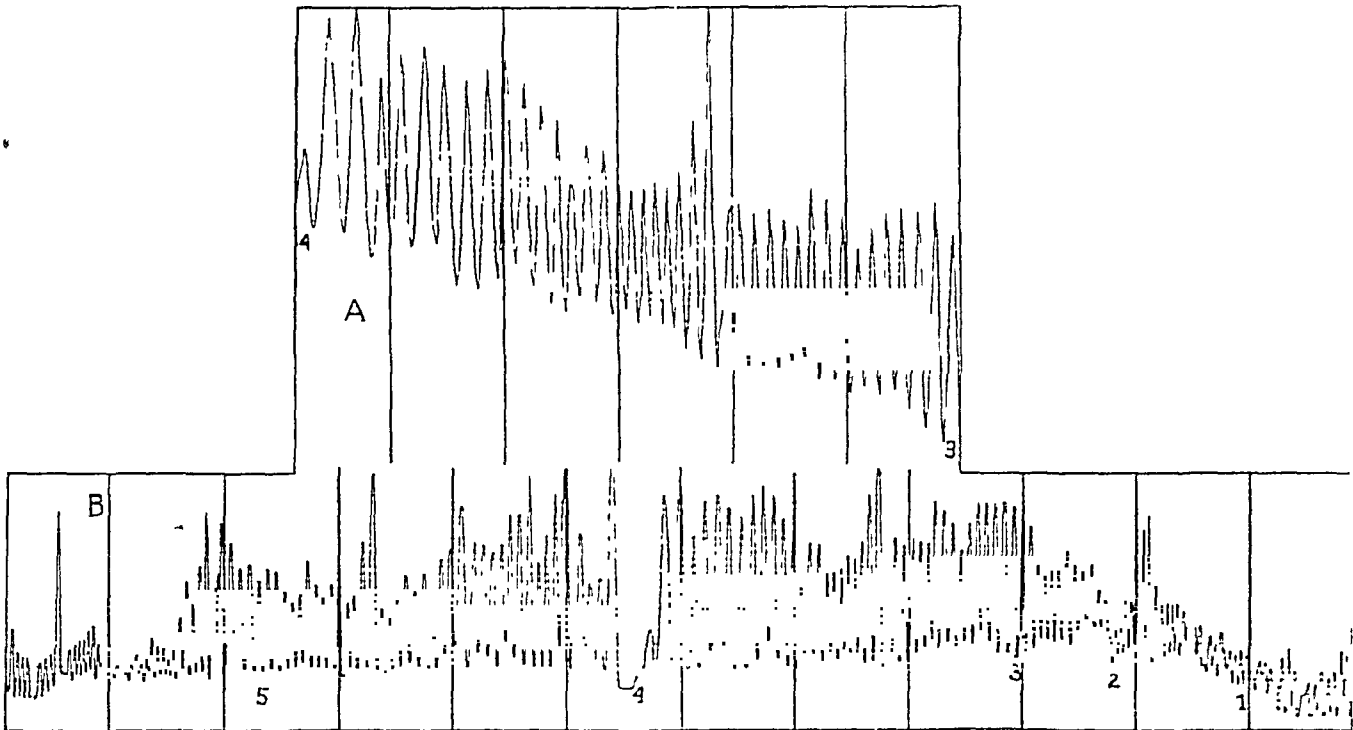


Chart 2.—Extreme increase in the amplitude of the respiratory movements and in the expiratory position of the chest after application of the nose-clip.

character of the respiratory movements disappeared in two subjects during examinations, but reappeared in one of them during a subsequent examination. It persisted in the remaining three. Respirations with sighing were present in two subjects and persisted during the metabolic test. The rhythm was unaltered during the remaining twenty-five examinations.

The expiratory position of the chest increased during the metabolic determination in five examinations of four subjects. The increase began in each subject when the mouthpiece was inserted and in three instances the position remained constantly elevated after the nose-clip was applied. At the end of the metabolic test, the expiratory volume of the chest returned to the previous level, as shown in charts 2 and 3.

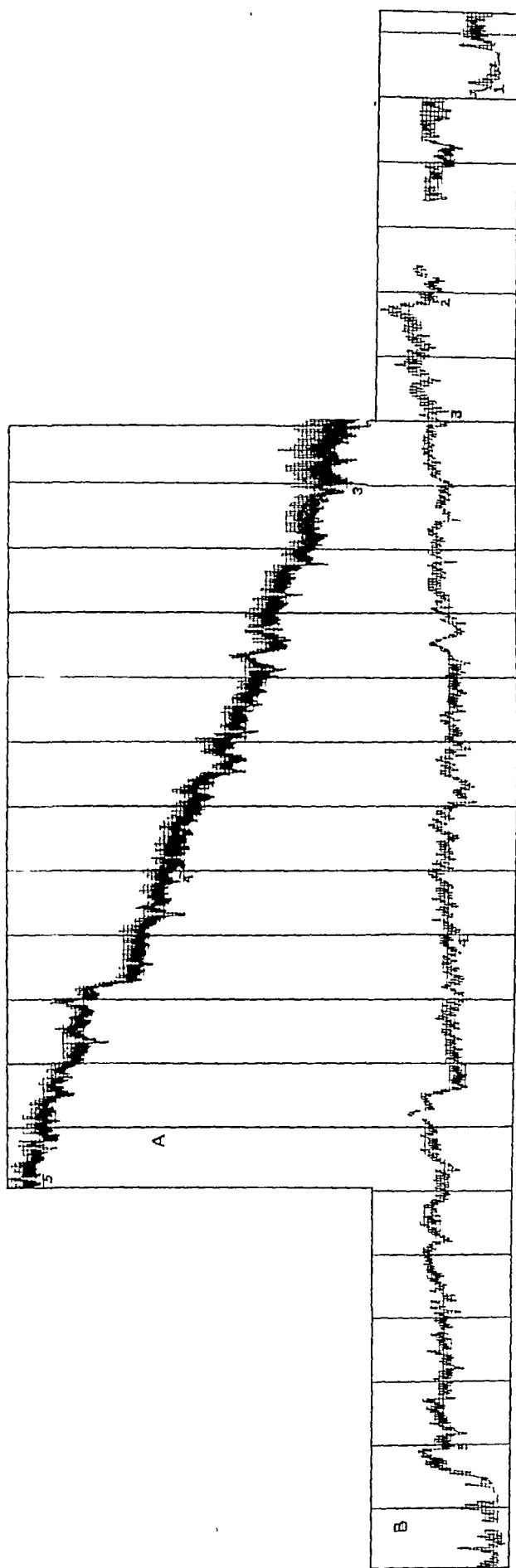


Chart 3.—Increase in the expiratory position of the chest during determination of the metabolic rate.

In one subject the expiratory position continued to increase during the first period of the metabolic study, but decreased during the second period, as shown in chart 4.

The primary function of external respiration is the proper ventilation of the lungs, that is, to keep sufficient oxygen available in the alveolar air and, by discharging the carbon dioxide, to maintain the proper tension. Alterations in the rate or in the amplitude of the respiratory movements therefore do not indicate alterations of the respiratory function unless they affect the rate of ventilation of the lungs. The relative volume of ventilation was determined from the plethysmograms by adding the individual inspiratory volumes for several minutes before the test, and comparing the sum with that of the inspiratory volumes for a similar time during the test. So long as the expiratory position of the chest remained constant, the respiratory quotients were approximately normal when the rate of ventilation was normal or slightly increased, and elevated when this was moderately or markedly increased. The ventilation was increased in thirty examinations. In twenty-two instances it was increased by a change in amplitude alone; in five it was increased because of an increase in amplitude in spite of a decrease in rate; in two subjects the increase in ventilation accompanied an increase in both amplitude and rate. Another showed an increase in ventilation with increases in amplitude, rate and expiratory position. During one study the ventilation was not changed, since, although the amplitude increased, the rate decreased proportionately.

The ventilation during three examinations in subjects 7 and 23 is difficult to appraise. In subject 23 the rate was not altered, the amplitude decreased slightly, the expiratory position of the chest increased markedly during the first period of the metabolic study, and the amplitude increased slightly with a reduction in the expiratory position without change in rate during the second period (chart 4). During the first period oxygen was stored in the lungs, and carbon dioxide was retained, owing to an increase in the expiratory volume of the chest. Some oxygen which was not utilized was therefore removed from the spirometer, and some carbon dioxide which was produced remained in the lungs and was not measured. This combination of circumstances led to a respiratory quotient of 0.37 during the first period. In the second period, the volume of the chest decreased, the stored oxygen was utilized, and the accumulated carbon dioxide was exhaled and measured, so that a respiratory quotient of 1.77 was obtained. However, the respiratory quotient for the combined period was 0.83, which indicated that the changes in ventilation equalized each other. The changes in this subject are admittedly extreme, and the appearance of the spirographic tracing would indicate that the test was unsatisfactory; but the same type of change in the expiratory position of the chest, if



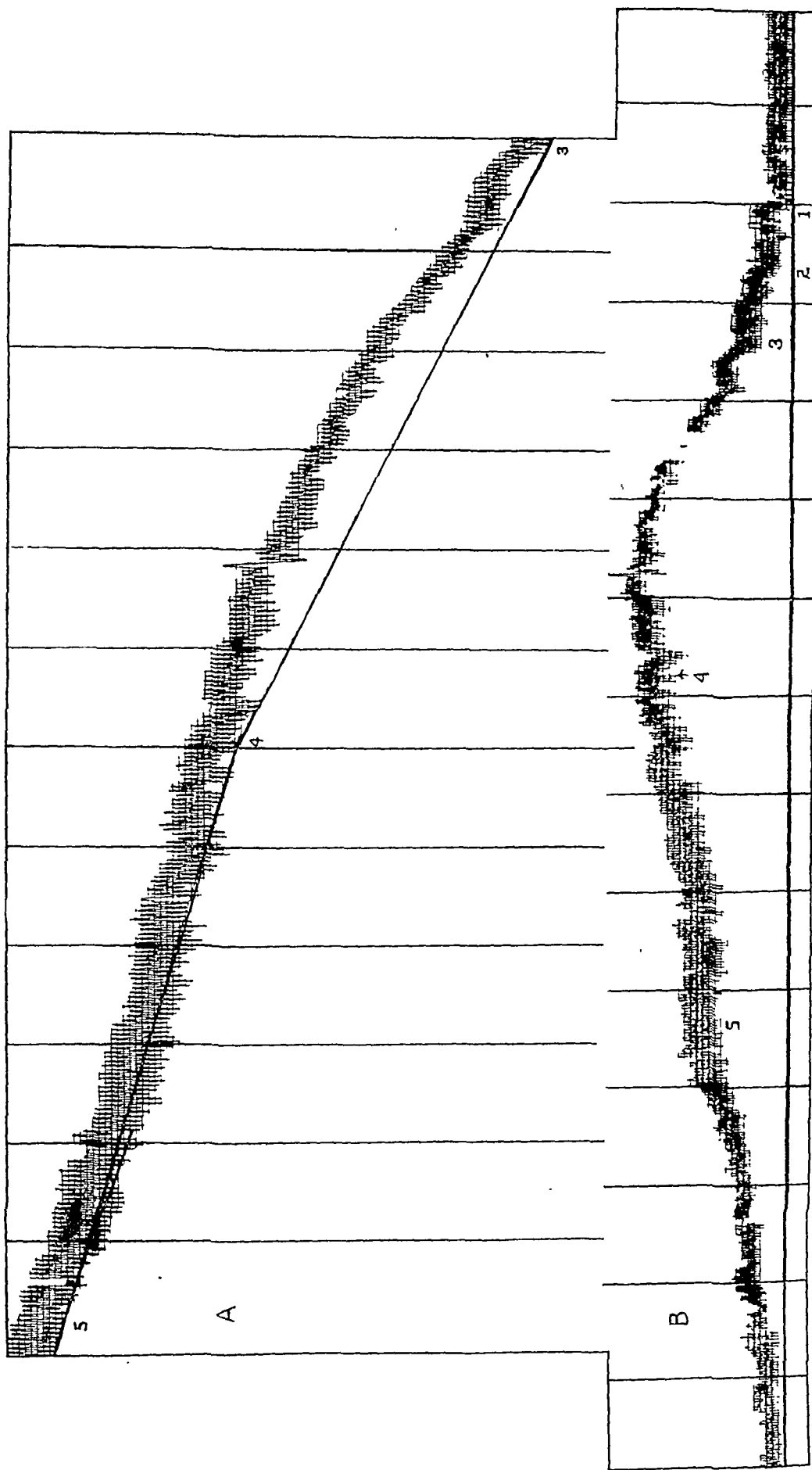


Chart 4.—Marked increase in the expiratory position of the chest during the first period of the metabolic study, followed by a decrease during the second period.

less marked, might easily go unrecognized were it not for the plethysmographic record. Subject 7 exhibited an increase in the expiratory position of the chest without alteration in the rate or amplitude and maintained a low respiratory quotient throughout the test. The respiratory quotient in the second period was lower than that in the first, and on both occasions was below 0.7.

In the group of normal subjects, two who were trained reacted by an increase in amplitude alone. The third, who was familiar with the procedure but who had never been a subject, showed an increase in amplitude and expiratory position of the chest, with a decrease in rate and a change in rhythm.

The basal metabolic rate of eleven of the patients had been determined previously; some of them showed as marked alterations in the respiratory movements as patients not familiar with the procedure. The same subject may show a different reaction during successive tests, as illustrated by patients 6 and 8 (table 1). Patient 6 showed no change in rate during one examination, but demonstrated an increase in a subsequent test. Patient 8 showed a change in rhythm during one test and none during a subsequent study. Patient 7 showed a variety of irregularities; the spiographic tracings (chart 5) are obviously too irregular to be of value in determining oxygen consumption. The greatest changes were in amplitude and in the expiratory position of the chest. Chart 3 shows simultaneous spiographic and plethysmographic records for this patient. Variations in the expiratory position of the chest are present, but the position is approximately the same at the end as at the beginning. The measured oxygen consumption would therefore appear to be reliable, except that irregular breathing entails more muscular effort than normal, quiet breathing. This patient exhibited changes in the respiratory movements whenever his attention was directed to his breathing.

#### THE INFLUENCE OF THE ALTERATIONS OF THE RESPIRATORY MOVEMENTS ON THE CALCULATED BASAL METABOLISM

The influence of alterations in the respiratory movements on the results of the basal metabolic tests was also studied. Increases in ventilation due to changes in the rate or the amplitude, or both, do not materially alter the consumption of oxygen, as Carpenter has shown. In five studies on four subjects as well as in one subsequent observation there was a significant change in the expiratory position of the chest during the determination of the basal metabolic rate. Such an alteration of the respiratory movements may cause the apparent basal metabolic rate to be increased or decreased. Should an increase in the expiratory position occur before the test, with a decrease during the test, as evidently was the case with Carpenter's<sup>2</sup> subject who added gas to the

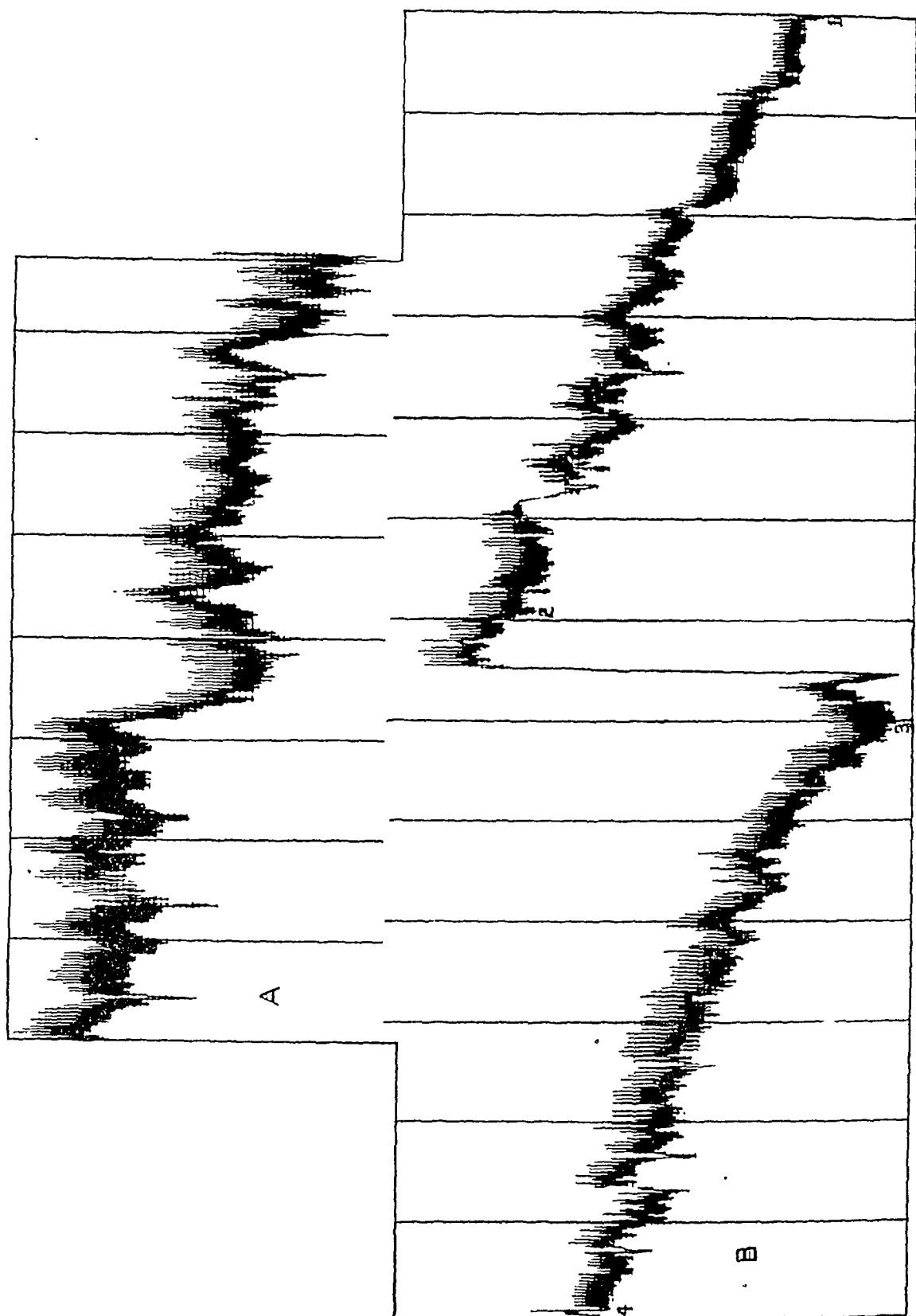


Chart 5.—Spirographic records of patient 7. At 1 the expired air was diverted through weighed absorptive containers; at 2, to unweighed absorptive containers, and at 3, to weighed absorptive containers. The test ended at 4.

spirometer, the result would be too low. If the increase occurs before the test and is maintained, the results will be unaltered. If the expiratory position increases during the test, the results will be too high.

In table 2 are tabulated the diagnoses, the relations of the changes in the expiratory position of the chest to the metabolic test, the respiratory quotients and the results of the determinations of the basal metabolic rate in percentages of normal.

In subject 3 the expiratory position of the chest increased when the mouthpiece was inserted but remained constantly elevated throughout the test, decreasing afterward. The ventilation was increased, as shown by the respiratory quotient and the great increase in amplitude. The graphs are shown in chart 2.

TABLE 2.—*Changes in Expiratory Position of Chest During Determination of Basal Metabolic Rate in Six Persons*

Case	Diagnosis	Effect of Mouth-piece	Effect of Nose-Clip	Change During Test	Respi-ratory Quotient	Change After Dis-continuing Test	B.M.R., per Cent
3	Normal.....	Increased	No change	No change	0.90	Decreased	
7	Effort syndrome						
	Period I.....	Increased	Increased	No change	0.62	.....	+ 7
	Period II.....	.....	.....	No change	0.54	Decreased	+ 8
7	Effort syndrome						
	Period I.....	Increased	Increased	No change	0.62	.....	- 4
	Period II.....	.....	.....	Increased	0.44	Decreased	+31
18	Diabetes (mild)						
	Period I.....	Increased	Increased	Increased	0.61	.....	+73
	Period II.....	.....	.....	No change	0.63	Decreased	+22
23	Pulmonary tuberculosis (after thyroidectomy)						
	Period I.....	Increased	Increased	Increased	0.37	.....	+47
	Period II.....	.....	.....	Decreased	1.77	Decreased	-15
24	Hyperthyroidism (?)						
	Psychoneurosis (?)						
	Period I.....	Decreased	Increased	Decreased	....	.....	- 2
	Period II.....	.....	.....	No change	....	Decreased	+34

During the first study of subject 7, the expiratory position of the chest increased after the mouthpiece was inserted and again after the nose-clip was applied. Although the expiratory position fluctuated during both periods of the test, it was at the same level at the beginning and at the end, and the results of the metabolic tests were within normal limits. The graphs are shown in chart 3. In a subsequent study with this subject, the expiratory position was constantly elevated throughout the first period, but decreased between the first and second periods and increased during the second period. The increase of the expiratory position of the chest increased the calculated metabolic rate for this period 27 per cent (table 2).

In subject 18, the expiratory position of the chest increased during the first period, and remained almost constant throughout the second period. This alteration increased the apparent basal metabolism 51 per cent (table 2).

In subject 23, the expiratory position of the chest increased during the first period and decreased during the second period. The difference in the calculated results of the two periods was 62 per cent. If one calculated the results on the basis of a twelve-minute test period instead of two six-minute periods, the basal metabolic rate would become +16 per cent. According to the plethysmographic record, 250 cc. of oxygen was stored in the lungs at the end of the test period. If the quantity of oxygen removed from the spirometer were reduced by this amount, the basal metabolic rate would be +6.9 per cent and the respiratory quotient for the twelve-minute period, 0.85. The graphs are shown in chart 4.

In subject 24 (table 2), the expiratory position of the chest increased when the nose-clip was applied, decreased during the first period and was not materially altered during the second period. The difference between the results of the two periods is 36 per cent. The graphs are shown in chart 6.

Variations in the excretion of carbon dioxide when the closed circuit method is employed have been noted by Carpenter and several other investigators. The increased excretion has been attributed to an increased ventilation of the lungs, as illustrated by subject 3, but no good explanation has been given for the occasional decreased excretion.

During both studies of subject 7 and during the first period of study of subject 23, the respiratory quotients were low. This apparent decrease in the excretion of carbon dioxide may be attributed to the increased volume of the lungs without a proportionate increase in the rate or in the amplitude of breathing. Such circumstances allow carbon dioxide to accumulate in the lungs, as was shown in subject 23. Alterations in the expiratory position of the chest, however, do not explain the decreased carbon dioxide excretion in all subjects, as shown by subject 18, in whom the ventilation of the lungs increased. Furthermore, low respiratory quotients have been observed when the expiratory position was unaltered.

It is commonly believed by physicians and by laboratory workers that all errors in studies of metabolism by the closed circuit method tend to increase rather than decrease the apparent basal metabolism. But if the expiratory position of the chest decreases during the test, the results will be too low, as illustrated by subjects 23 and 24. It must be said, however, that any physician who is familiar with the problems encountered in the determination of the basal metabolic rate would be very doubtful of the results calculated from the graphs cited, with the possible exception of that for the second period of study of subject 23. There is no doubt that numerous reported results have been calculated from similar graphs, and these changes in the volume of the chest may account

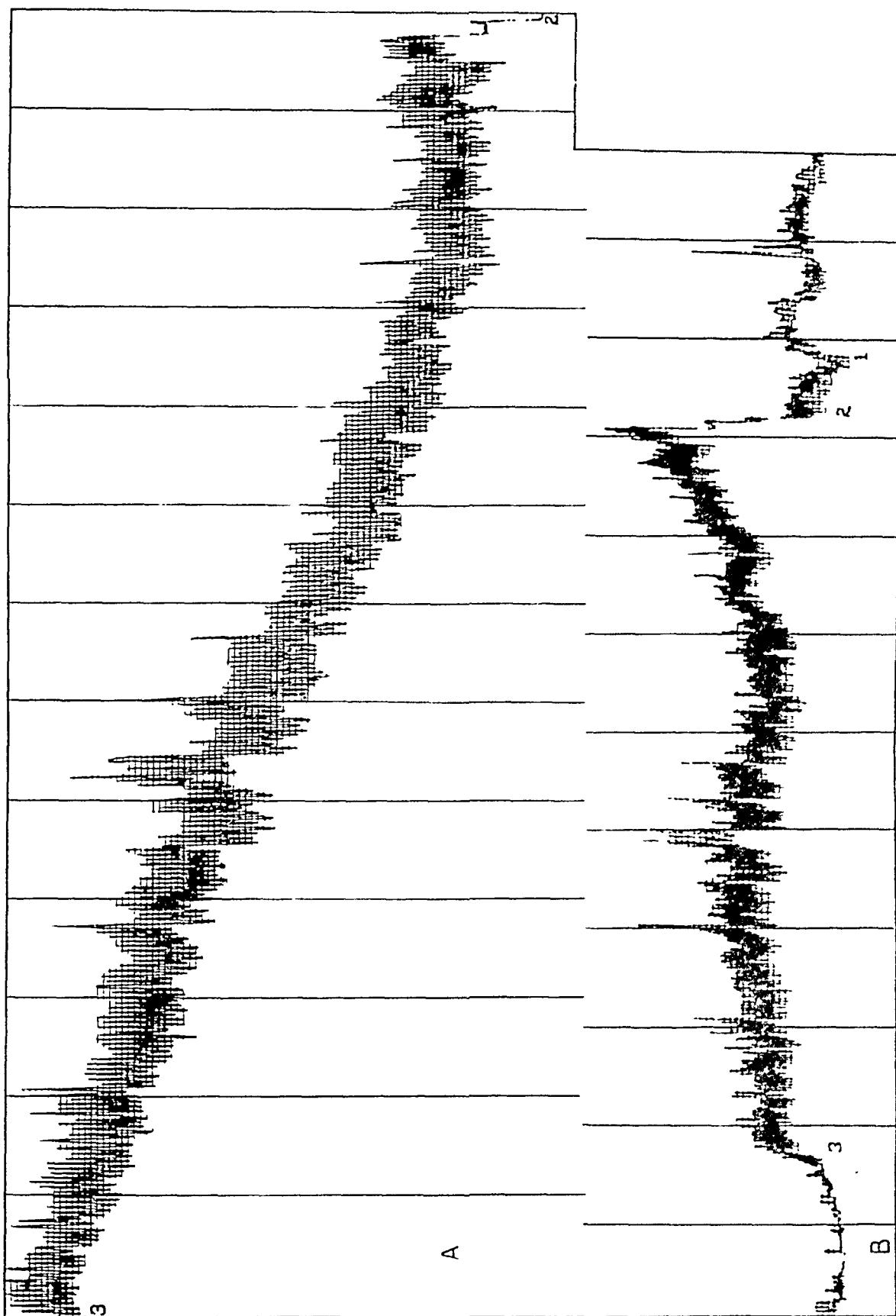


Chart 6.—At 1 the mouthpiece was inserted; at 2 the nose-clip was applied, and at 3 the metabolic test was discontinued. The carbon dioxide excreted was not determined.

for some of the fluctuating, elevated basal metabolic rates which are not in accord with the clinical findings.

The closed circuit method is the most practical clinical method for the determination of the basal metabolic rate. If test periods of from ten to twelve minutes are used, as was advocated by Benedict,<sup>3</sup> and Carpenter,<sup>2</sup> the alterations in the results attributable to changes in the expiratory position of the chest will be considerably decreased, as illustrated in subject 23.

#### SUMMARY

1. The influence of the determination of the basal metabolic rate on the respiratory movements has been studied in three normal and twenty diseased subjects.

2. The respiratory movements may be altered in rate, rhythm, amplitude or expiratory position of the chest, or in several combinations of these.

3. The respiratory movements were altered in every subject during the determination of the basal metabolic rate, and the ventilation was increased in twenty subjects, unchanged in one and questionably altered in two.

4. The manner in which the respiratory movements are altered varies with different subjects and may vary with the same subject during different examinations.

5. Changes in the expiratory position of the chest may alter the basal metabolic rate as determined by the closed circuit method.

6. The decreased excretion of carbon dioxide by some subjects in the basal state may be due in part to changes of the expiratory position of the chest.

7. Alterations of the expiratory position of the chest may explain some of the variances between the determinations of the basal metabolic rate and the clinical findings.

8. The alterations in the determinations of the basal metabolic rate due to changes of the expiratory position of the chest would be materially decreased if longer test periods were used.

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3. Benedict, F. G.: An Apparatus for Studying the Respiratory Exchange, *Am. J. Physiol.* **24**:345 (June) 1909; A Portable Respiration Apparatus for Clinical Use, *Boston M. & S. J.* **179**:667 (May 16) 1918.

# BENIGN AND MALIGNANT NEUTROPENIA

## PRESENT STATUS OF KNOWLEDGE OF THIS CONDITION. WITH REPORT OF FOUR CASES

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Even now, thirty-two years after the first recorded observations on neutropenia, there is considerable confusion, some investigators refusing to admit its existence as a true disease entity. There is ample reason for this. On reading over the published case reports, it soon becomes evident that they deal with a group of diseases and not with a single disease. The group now includes any condition showing leukopenia and neutropenia, no matter what the cause or the clinical picture.

The clinical features, including symptomatology, physical observations, pathology and treatment, are abundantly described in the literature, but one must read many publications before all phases of the disease can be fully covered or the information sought obtained. Important textbooks and systems of medicine contain only a brief discussion of the condition. This paper, arranged in more or less textbook fashion, represents a review of the established observations.

### DEFINITION

Neutropenia is a grave disease of unknown etiology characterized by a marked reduction in the total number of white cells and a great reduction in the percentage of granulocytes, accompanied by aplastic, normal or hyperplastic myeloid tissue. Following the peripheral neutropenia there may be any number of lesions and symptoms which might follow the removal from the body of such an important defense mechanism. The disease may be acute or chronic.

### NOMENCLATURE

Werner Schultz, in 1922, proposed the name agranulocytosis. The supply of hematologic terms is so abundant that there is little excuse for choosing such an ambiguous one. This term came into the nomenclature, no doubt, on account of its brevity. It is incorrect. The name agranulocyte was originally chosen for "neutrophils without granulations" seen in blood smears from cases of leukemia. By "agranulocytosis" is meant an increase in these atypical neutrophils, which is not



intended. Friedemann<sup>1</sup> being impressed by the usual severe localization of the process in the throat, suggested the name "angina agranulocytica." This name is unfortunate also, because of its intrinsic ambiguity, and because it implies that one is dealing with an infection of the mouth which causes neutropenia instead of with a syndrome of utterly unknown etiology. It is now known, also, that cases do occur without angina. Because of these confusing terms, many others have been suggested, such as mucositis necroticans agranulocytica, sepsis with granulocytopenia, monocytic angina, granulocytopenia and agranulosis. Baldrige and Needles proposed the term "idiopathic neutropenia," which seems to be a most descriptive and appropriate name. Schilling<sup>2</sup> suggested the name "malignant neutropenia." Rosenthal,<sup>3</sup> in his classification made according to the clinical manifestations and course, divided neutropenia into malignant (fatal) and benign (recovered) cases. It might be well further to divide these into two main classes as follows: (1) primary benign and primary malignant neutropenia, the true cases of benign and malignant neutropenia, in which the etiology is unknown; (2) secondary benign and secondary malignant neutropenia, the cases in which the etiologic agents are evident or in which one is dealing with examples of well recognized clinical entities.

#### HISTORY

If malignant neutropenia had existed to any great extent prior to 1922, it undoubtedly would have been described long before, since the disease runs such a dramatic course and usually terminates fatally. Blood counts have been made as a routine procedure in most large hospitals for the past fifty years. Pepper,<sup>4</sup> in his history of malignant neutropenia, stated that standard laryngologic works of fifty years ago apparently described this disease under the heading "putrid sore throat" and "gangrenous angina," and he said that Mackenzie, in his manual of diseases of the throat and nose, credited Gubler, in 1857, and Trousseau, in 1865, with having clearly distinguished the disease from diphtheria. In 1902, Brown<sup>5</sup> reported a fatal case of acute primary infectious pharyngitis with extreme leukopenia. This probably was the first case reported in this country. Türk<sup>6</sup> reported one case in 1907.

1. Friedemann, U.: *Med. Klin.* **19**:1357, 1923.

2. Schilling, V.: *The Blood Picture and Its Clinical Significance*, translated by R. B. H. Gradwohl, eds. 7 and 8, St. Louis, C. V. Mosby Company, 1929.

3. Rosenthal, N.: *Am. J. Clin. Path.* **1**:7 (Jan.) 1931.

4. Pepper, O. H. P.: *The History of Agranulocytic Angina*, J. A. M. A. **97**:1100 (Oct. 10) 1931.

5. Brown, P. K.: *Am. Med.* **3**:649 (April) 1902.

6. Türk, W.: *Wien. klin. Wchnschr.* **20**:157, 1907.

Leale,<sup>7</sup> in 1910, reported a case in a male child 2½ months old under the title, "Recurrent Furunculosis in an Infant Showing an Unusual Blood Picture." Baldridge and Needles<sup>8</sup> reported a case that occurred in 1910, pointing out that in former years it either was overlooked because the blood was not examined, or was interpreted as a symptom of exhaustion of the bone marrow, aleukemic leukemia or aplastic anemia. In 1922, Schultz<sup>9</sup> reported four cases, describing the clinical syndrome to which he applied the term "agranulocytosis," and he stated the belief that it was a distinct clinical entity. From that date interest in this symptom complex has continually increased. In 1923, Friedemann<sup>1</sup> published an article pointing out the frequent occurrence of angina in these cases. The case reported by Lovett<sup>10</sup> in 1924 stimulated interest in this disease in this country, and since that date many cases have been reported and many theories as to the pathogenesis and treatment suggested.

#### PHYSIOLOGY

Much of the accuracy in interpretation of the blood picture in this disease is dependent on an understanding of the underlying mechanism of hematopoiesis. It is with this in mind that I offer a review of the physiology of granulopoiesis, since it is with this portion of the hematopoietic tissue that one is concerned in this disease. On the basis of this knowledge of the physiology of granulopoiesis, a theory of pathogenesis may be formulated.

*Location of Granulopoietic Tissue.*—The granulopoietic tissue in the adult is located in the red marrow which is to be found in the ribs, the vertebrae, the sternum, the bones of the skull and the os innominatum. It is in the red marrow that granulopoiesis takes place normally.

*Size of the Granulopoietic Organ.*—The subject of bone marrow as a hematopoietic organ means the consideration of the entire marrow as a unit. It is an organ of no inconsiderable size, having been shown by Wetzel<sup>11</sup> to have a volume, in the adult human being, of 1,419 cc., which is thirteen times that of the spleen and almost equal to that of the liver. This whole structure will be found in a relatively uniform state under normal conditions. This means that the proportion of erythropoietic to granulopoietic tissue, as well as the proportions of the different levels of maturation within the two groups, is relatively con-

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7. Leale, M.: Recurrent Furunculosis in an Infant Showing an Unusual Blood Picture, J. A. M. A. **54**:1854 (June 4) 1910.

8. Baldridge, C. W., and Needles, R. J.: Am. J. M. Sc. **181**:533, 1931.

9. Schultz, W.: Deutsche med. Wchnschr. **48**:1495, 1922.

10. Lovett, B. R.: Agranulocytic Angina, J. A. M. A. **83**:1498 (Nov. 8) 1924.

11. Wetzel, G.: Verhandl. d. Anat. Gesellsch., Jena, 1920, p. 82.

stant. According to studies by Doan and Zerfas,<sup>12</sup> in three accident cases the ratio of erythropoiesis to granulopoiesis was 1:20, 1:16 and 1:5.5. Other authors have given a ratio of 1.3. It can thus be roughly estimated that from three to twenty times more tissue is devoted to the production of granulocytes than to the production of erythrocytes, or, in other words, the volume of the granulopoietic tissue is from nine and one-half to twelve times that of the spleen. In contrasting this with the great excess of erythroid over myeloid cells in the blood stream, the reverse in the ratio must be correlated with the greater length of survival of the erythrocytes in the blood stream. It would seem from this that the granulopoietic organ is manufacturing an extremely fragile and delicate product.

*Circulation of the Bone Marrow.*—This is accomplished by the main nutrient artery and its accompanying veins, passing toward either epiphysis, and its capillary branches to the venous sinusoids, together with numerous anastomoses of this system with the small vessels of the bone along the shaft and with larger epiphyseal vessels in the mature bone. The capillaries that lead directly from the nutrient arteries of the third and fourth order, the "transition capillaries" of Doan, are not the functioning capillaries, as in other organs, but rather they lead into tufts of sinusoids. These sinusoids constitute the functioning vascular bed of the marrow; they have walls like capillaries and appear like them when collapsed, but when open they have the diameter and lumen of large veins. The nature of these vessels was analyzed by Minot<sup>13</sup> in 1900, who introduced the term "sinusoid." When the sinusoids are dilated, there is a sluggish flow of blood, which brings the maturation factors to the right concentration for the white cells. Along the border of the marrow there is a narrow zone where the blood vessels of the marrow anastomose with those of the shaft of the bone. As granulopoiesis begins, every vessel of this narrow border is patent to the circulation; that is to say, there are no collapsed intersinusoidal capillaries. No other area of the marrow has so constantly a maximum supply of blood.

*Where Granulocytes Arise.*—The granulocytes arise outside of the blood vessels and pass into them by their own motility. They develop around the patent, dilated sinuses or vessels of the hematopoietic tissue in the peripheral, vascular zone, and move toward their borders as they become more mature. The young granulocytes exist here in groups at the same stage of maturation and fill the sinuses. They are seen to move en masse against the walls of the capillaries until the wall is bent

12. Doan, C. A., and Zerfas, L. G.: J. Exper. Med. **46**:511, 1927.

13. Minot, G. R.: Proc. Boston Soc. Nat. Hist. **29**:185, 1901.

inward. When the stretching reaches a certain point, a leukocyte close to the wall flows in between two endothelial cells and the rest follow in rapid succession.

For this brief outline it is deemed impracticable to attempt a description of each cell. For a complete study of the bone marrow, see Sabin's article,<sup>14</sup> from which this information has been derived. By following the accompanying diagram, I hope the brief text will be intelligible and a clear knowledge obtained.

*Maturation of Granulocytes.*—The cell from which granulocytes develop (parent cell) is a subject on which there is a difference of

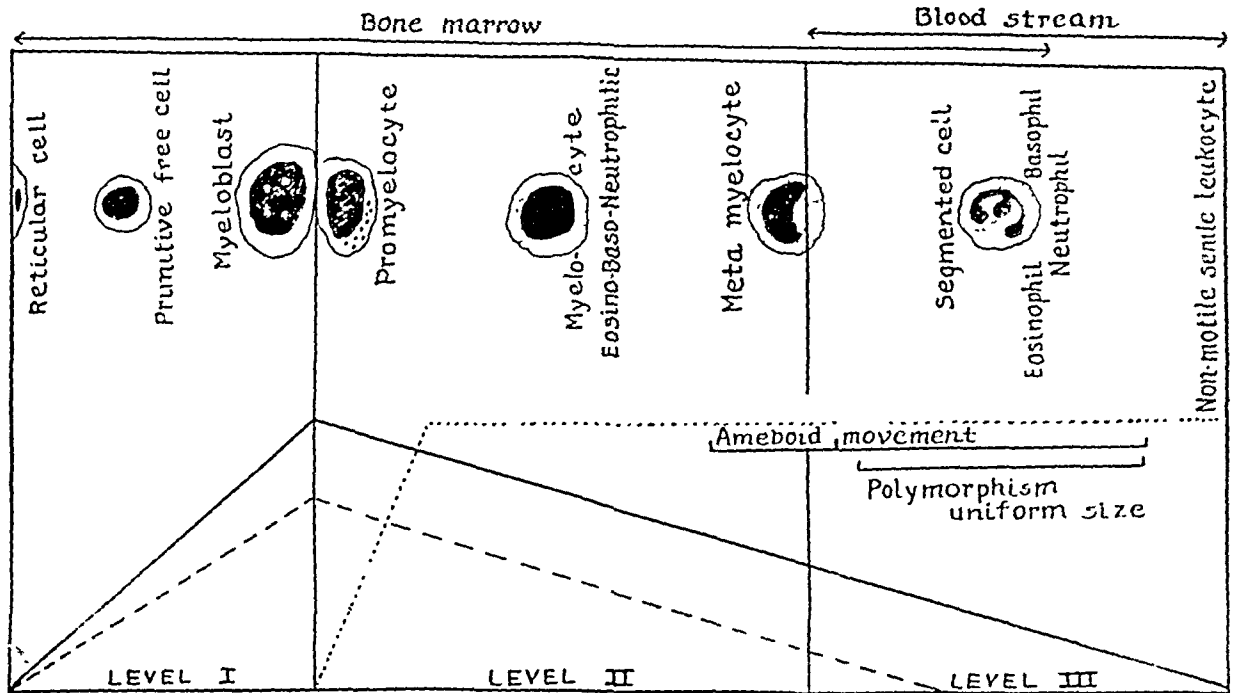


Diagram of the maturation of granulocytes, the cells being divided into three levels. The continuous curve indicates mitochondria; the dash curve, basophilia in the cytoplasm; the dot curve, granulations.

opinion. According to Sabin, this primitive cell is a reticular cell found in the interstices between the fat cells of the marrow.

**Level I:** This cell, with repeated divisions, gives rise to a primitive free cell. As the basophilia of the cytoplasm and the numbers of the mitochondria of this free cell reach a maximum, the cell becomes a myeloblast. This is a period of growth and division, and the primitive free cell of small size is found in the largest numbers. By the processes of basophilia and mitochondria the myeloblasts develop into promyelocytes and that is level II.

**Level II:** With the changing chemistry of the granules of the cytoplasm of the promyelocytes, eosinophilic, basophilic and neutrophilic

14. Sabin, F. R.: *Physiol. Rev.* 8:191, 1928.

myelocytes develop. This changing chemistry of the granules continues to the senile leukocyte stage, shown by the dotted line in the diagram. In level II, granulation increases as mitochondria and basophilia in the cytoplasm decrease. Cell division ceases in level II. Basophilia may be carried over into the cells of the circulating blood, especially in rapidly developing leukocytosis. This is shown by the broken line in the diagram. Sabin distinguished three stages in the development of the myelocytes according to their granulations, and designated them A, B and C; A is the youngest myelocyte and C the oldest myelocyte ready to develop into the metamyelocyte. When the myelocytes are fully formed, there is the onset of ameboid movements, and these cells are termed metamyelocytes (juvenile form of Schilling). Ameboid movement may begin a little before the metamyelocyte stage or almost at the end of it. The metamyelocytes may appear in the blood stream, 1 per cent being considered by Schilling as normal. Hence, the line indicating the end of level II and the beginning of level III is drawn through the metamyelocyte.

Level III: From the metamyelocytes are formed cells of approximately uniform size and content of specific granulations, and ameboid activity is at its height. These are the basophils, eosinophils and neutrophils ready to be delivered to the blood stream. In level III, the cells show functional maturity with a uniformity in size. Division no longer takes place, having ceased in level II, and polymorphism occurs. The leukocytes, according to Arneith, become more mature in the circulating blood, involving nuclear changes, and finally pass into the nonmotile phase; the cells in this stage are the fragile forms with easily ruptured membranes seen in fixed films.

*Rhythmic Delivery of Granulocytes.*—The rhythmic delivery of granulocytes from the marrow to the blood stream has been demonstrated by Sabin and her co-workers.<sup>15</sup> Shaw<sup>16</sup> demonstrated that the afternoon rise is but a part of a diurnal rhythm, with a second rise about midnight. This rhythmic delivery of cells persists in cases with leukopenia and leukocytosis, being particularly striking in the latter. The approximate hourly delivery of cells to the blood stream suggests that the time for the maturation from metamyelocyte to granulocyte might be expressed in units of hours or minutes, while the time for the maturation from promyelocyte through to metamyelocyte may possibly be expressed in units of days, probably from three to seven. With the concept in mind that bone marrow, as a hematopoietic organ, is the place where granulocytes are made, that it holds a large store almost ready

15. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindvall, J. A.: Bull. Johns Hopkins Hosp. **37**:14 (July) 1925.

16. Shaw, A. F. B.: J. Path. & Bact. **30**:1, 1927.

for delivery and that its store of immature forms is small in numbers but with exceedingly high potentiality toward multiplication, growth and maturation, the question of the mechanism to maintain such a normal structure becomes a major problem of hematology. Two different processes must be analyzed: first, the mechanism of the delivery of cells to the circulation, and second, the mechanism of maturation.

*Mechanism of Delivery.*—The question of how great a part vasomotor influences play in the mechanism of delivery is uncertain. Experiments concerning the response of the marrow to nerve stimuli have not been sufficiently controlled with reference to the normal rhythm of delivery to allow the forming of any definite conclusions.

There is more definite information available concerning chemotactic factors. It is possible to call the cells from the marrow by administering inactivated typhoid bacilli, depleting the bone marrow of myelocytes and leaving only promyelocytes and myeloblasts. This experiment was performed by Doan and his associates,<sup>17</sup> and can be expressed as representing a condition due to a chemotactic factor minus a maturation element. The cells of the marrow showed no toxic effect, and the marrow readily regenerated after the experiment. Of the many substances that have been shown to call leukocytes from the bone marrow, nucleic acid is most likely to be a part of the normal mechanism. An excellent contribution on this subject is that of Doan and others,<sup>18</sup> in a study of the effect of large doses of nucleic acid. Their study of the bone marrow showed clearly the chemotactic effect of the nucleic acid, with the massing of leukocytes around the patent sinusoids, a marked diapedesis into the vessels and the vacant areas of the marrow from which the granulocytes had been drawn. They also found that the granulocytes could be called from the marrow by the split products of nucleic acid, the purine bases, adenine and guanine. It is thus likely that nucleic acid and its derivatives are important physiologic factors in the chemotactic reaction, and that the showers of nonmotile leukocytes in the circulating blood may give a rhythmic discharge of such products (nucleic acid, adenine, guanine, etc.) into the circulation. In later experiments on nucleic acid and its degradation products, Doan<sup>19</sup> gave the following conclusions:

1. Nucleic acid and its degradation products exert a chemotactic effect on normal myeloid foci with a prompt effective increase in the delivery of granular leukocytes to the peripheral circulation under a controlled physiologic or rhythmic

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17. Doan, C. A.; Cunningham, R. S., and Sabin, F. R.: *Contrib. Embryol.* **16**:163, 1925.

18. Doan, C. A.; Zerfas, L. G.; Warren, S., and Ames, O.: *J. Exper. Med.* **47**:403 (March) 1928.

19. Doan, C. A.: *The Neutropenic State*, *J. A. M. A.* **99**:194 (July 16) 1932

mechanism. 2. Repeated large intravenous injections tend neither to exhaust nor to cause a malignant hyperplasia of the myeloid elements in normal animals. 3. A short course of injections stimulates a myeloid hyperplasia of normal marrow without otherwise injurious consequences, which is reflected by a relative and absolute increase in the amphophilic granulocytes in the blood stream of rabbits.

Of maturation factors there is but meager knowledge, but those bacteria that produce a sustained leukocytosis introduce such a factor as they produce an increased division, growth and maturing of the less mature leukocytes in the marrow far beyond the normal amount. Bacon and his co-workers<sup>20</sup> considered that even in infections the stimulus to an increased activity of the marrow comes from altered body proteins. The relationship of the degree of leukocytosis to the resistance of the animal in infections has been repeatedly confirmed since Metchnikoff, and thus, as long as none of the substances involved in these reactions is known, variations in the response of the animal must be studied in terms of the amount of the infection and possibly differences in the power of the hematopoietic tissues to respond. One might venture to speculate, though, that the resistance of the patient may not depend on the power of the granulopoietic tissue to respond, but on the power of the tissues producing the maturation factor to respond. The only definite knowledge of maturation factors concerns erythrocytes. The recent application of the liver diet to patients with pernicious anemia and the isolation from liver of the specific substance by Cohn and his associates<sup>21</sup> involve the discovery of a maturation factor. Minot and Murphy<sup>22</sup> have shown that by the liver diet the normal mechanism is restored by the speedy appearance in the peripheral blood of reticulated erythrocytes of normal size. Liver extract does not supply a maturation factor for granulocytes. No doubt there is a similar maturation factor in the body to regulate the normal production of granulocytes. The modern aspect of this problem involves an investigation of the chemical maturation factors which determine the granulocytes. These chemical factors are to be sought in certain organ extracts, as well as in specific dietary factors some of which may be vitamins.<sup>23</sup>

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20. Bacon, D. K.; Novy, F. O., and Eppler, H. H.: Factors in Leukocytosis, *Arch. Int. Med.* **30**:229 (Aug.) 1922.

21. Cohn, E. J.; Minot, G. R.; Fulton, J. F.; Ulrichs, H. F.; Sargent, F. C.; Weare, J. H., and Murphy, W. P.: *J. Biol. Chem.* **74**:69, 1927.

22. Minot, G. R., and Murphy, W. P.: *Boston M. & S. J.* **195**:410, 1926; *Treatment of Pernicious Anemia by a Special Diet*, *J. A. M. A.* **87**:470 (Aug. 14) 1926.

23. Whipple, G. H.; Robscheit-Robbins, F. S., and Hooper, C. W.: *Am. J. Physiol.* **53**:236, 1920. Robscheit-Robbins, F. S., and Whipple, G. H.: *ibid.* **72**:408 and 431, 1925. Drew, A. H., and Mottram, J. C.: *Lancet* **2**:1202, 1921. Koessler, K. K., and Maurer, S.: *Treatment of Pernicious Anemia with a High Caloric Diet, Rich in Vitamins*, *J. A. M. A.* **89**:768 (Sept. 3) 1927. Cohn, Minot, Fulton, Ulrichs, Sargent, Weare and Murphy.<sup>21</sup> Minot and Murphy.<sup>22</sup>

*Function of Neutrophils.*—Roberts and Kracke<sup>24</sup> said: "We have evidence that the mere loss of granulocytes for seven days is incompatible with life." Their absence gives new slants and intimations on the part they play in immunity. Granulocytes are one of the chief sources of immunity. With their disintegration and released ferments they give much active daily immunity to the body. They are thought to be the source of complement, and complement is present in the plasma, owing probably to the continued disintegration of neutrophils. Complement is probably the most important single factor in the destruction of bacteria and the defense of the tissues. There is some evidence to show that granulocytes may be the chief source of supply for many of the various types of immune bodies, such as bacteriolysins, hemolysins and precipitins. The rôle of neutrophils in infections is well known.

*Normal Destruction of Neutrophils.*—Weiskotten,<sup>25</sup> experimenting with rabbits, showed that the life span of the neutrophil in the blood stream was about four days. The case studies by Roberts and Kracke<sup>24</sup> seem to prove that the life span of the human neutrophil is about the same. Some idea can thus be had as to the enormous numbers of granulocytes to be consumed daily, termed physiologic degeneration. Cells in the nonmotile phase appear in the blood stream in showers, indicating that there is death of many granulocytes in the blood stream. There are various physiologic outflowings of granulocytes from the blood into the tissues, with consumption in the tissues. There is elimination of neutrophils into the saliva and probably into the entire digestive tract and onto all mucous membranes. There is apparently a gradual loss of granulopoietic tissue with advancing years. Custer and Ahlfeldt<sup>26</sup> studied the tibia, the femur, rib, sternum and vertebra in a hundred unselected cases and found that the cellularity of these marrows decreased with advancing years of life, the decrease corresponding in rapidity to the order named. The response of these marrows to a hematopoietic stimulus of a given intensity is in the following order: vertebra, sternum, femur, rib and tibia.

#### THEORIES OF PATHOGENESIS

Explanation of the pathogenesis of this disease rests on hypothesis alone. In reviewing the literature one finds many explanations. I shall attempt to group these hypotheses so that they may be covered as briefly as possible.

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24. Roberts, S. R., and Kracke, R. R.: Agranulocytosis, J. A. M. A. **95**:780 (Sept. 13) 1930.

25. Weiskotten, H. G.: Am. J. Path. **6**:183, 1930.

26. Custer, R. P., and Ahlfeldt, F. E.: J. Lab. & Clin. Med. **17**:969 (July) 1932.



*Predisposing Causes.*—Neutropenia is seen most frequently in women. Hueper<sup>27</sup> found a ratio of three and one-half women to one man, or 77.5 per cent in women. In the final analysis, it may be found that neutropenia and leukopenia, chronic and acute, do not predominate in either sex. Roberts and Kracke<sup>28</sup> presented a table compiled from eight thousand leukocyte and differential counts which shows this trend in chronic cases, only 56 per cent being in female patients. Practically all of the typical cases of primary benign and malignant neutropenia have occurred in the fourth decade of life—from 41 to 58 years of age. Cases have occurred in children, in young adults and past the age of 60, but they are more rare. Under predisposing causes must also be mentioned the coincidence of previous disease of the liver and the gall-bladder with malignant neutropenia, which has been stressed by Hueper and Garrison<sup>29</sup> and other authors.<sup>30</sup> The majority of the cases of benign and malignant neutropenia reported have occurred in Germany and the United States. Other predisposing causes may be those drugs and chemicals containing the benzene ring, the arsenicals, mesothorium, trinitrotoluene, x-rays and the gamma rays of radium. Certain infections may also be predisposing cases. Cases coming under this heading are classed as secondary benign and secondary malignant neutropenia.

*Organisms as a Cause.*—Many authors<sup>31</sup> think that malignant neutropenia is an infectious disease, but attempts to reproduce malignant neutropenia by injecting into animals organisms isolated from lesions, from the bone marrow and from the blood stream of patients have failed to give conclusive information. A review of the literature discloses a large number of patients giving the history of Vincent's angina, trench mouth or the extraction of teeth prior to the clinical onset. Seiferth<sup>32</sup> reported a case of malignant neutropenia following tonsillectomy. These infections might be interpreted as a result and not a cause, as the

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27. Hueper, W. C.: Agranulocytosis (Schultz) and the Agranulocytic Symptom Complex, *Arch. Int. Med.* **42**:893 (Dec.) 1928.

28. Roberts, S. R., and Kracke, R. R.: *Ann. Int. Med.* **5**:40 (July) 1931.

29. Hueper, W. C., and Garrison, L. E.: *S. Clin. North America* **10**:407 (April) 1930.

30. (a) Schaefer, R.: *Deutsches Arch. f. klin. Med.* **151**:191 (May) 1926. (b) Aubertin, C., and Lévy, R.: *Arch. d. mal. du cœur* **21**:369, 1928. (c) Peritz, E.: *Zentralbl. f. Chir.* **54**:2129 (Aug. 20) 1927. (d) Hueper, W. C., and O'Conner: *Laryngoscope* **38**:679, 1928.

31. Feer, W.: *Agranulocytosis*, *Schweiz. med. Wchnschr.* **56**:551, 1926; abstr., *J. A. M. A.* **87**:366 (July 31) 1926. Weiss, J.: *Wien. Arch. f. inn. Med.* **14**:303 (May) 1927. Zadek, I.: *The Agranulocytosis Question*, *Med. Klin.* **21**:688 (May 8) 1925; abstr., *J. A. M. A.* **85**:77 (July 4) 1925. David, W.: *Med. Klin.* **21**:1229 (Aug. 14) 1925.

32. Seiferth, L. B.: *Deutsche med. Wchnschr.* **57**:1930 (Nov. 13) 1931.

patients may have been suffering from an unrecognized chronic granulopenia. The depression in the bone marrow in this disease may be caused by a hidden or a latent infection that has been present for a long time, the depressed marrow then being unable to cope with an emergency. Fried and Dameshek,<sup>33</sup> in their experimental work of producing neutropenia, infected rabbits with *Salmonella suispestifer* by way of the blood stream. By injecting small doses or overwhelming doses they could produce two types: (1) cases in which the animals recovered and (2) fulminating cases ending fatally. The blood picture showed leukopenia and neutropenia. In the cases in which recovery occurred the bone marrow showed areas of necrosis with patches of proliferation. In the fulminating cases there was but little evidence of myeloid proliferation. Piersol and Steinfield<sup>34</sup> found that a long-continued granulopenia could not be induced in healthy rabbits by the use of a small group of common bacteria. Marked leukopenia and neutropenia due to an infection (secondary neutropenia) should be distinguished from typical or primary neutropenia, in which the primary lesion is in the blood or the bone marrow or in both and infection follows the peripheral neutropenia. Therefore, the opinion that the organisms isolated in this disease are the cause does not seem to be well substantiated. It seems more likely that the organisms are secondary invaders growing profusely in a system devoid of granulocytes. It is not a new experiment to exhaust the bone marrow, one or all of its component parts, experimentally with various organisms, so that producing leukopenia and neutropenia experimentally with these agents is attacking the problem, at least from an etiologic standpoint, from the wrong angle.

*Septic and Toxic Processes.*—A number of authors have stated that the blood picture in benign and malignant neutropenia is due to a marked effect on the myeloid cells by a septic or a toxic process; others, that it is the exhaustion of normal bone marrow as the result of a non-specific sepsis.<sup>35</sup> Schultz<sup>9</sup> said that it is a disease per se, being caused by a specific agent that has a particular affinity for the myeloid system, but he did not state of what character the specific agent might be. Stocké<sup>36</sup> expressed the belief that malignant neutropenia is not a special disease, but an abnormal reaction to sepsis. Dameshek and Ingall<sup>37</sup>

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33. Fried, B. M., and Dameshek, W.: Experimental Agranulocytosis, *Arch. Int. Med.* **49**:94 (Jan.) 1932.

34. Piersol, G. M., and Steinfield, E.: Granulopenia (Granulocytopenia), *Arch. Int. Med.* **49**:578 (April) 1932.

35. Ehrmann, R., and Preuss, J.: *Klin. Wchnschr.* **4**:267 (Feb. 5) 1925.

36. Stocké, A.: *Folia haemat.* **40**:40, 1930.

37. Dameshek, W., and Ingall, M.: *Am. J. M. Sc.* **181**:502, 1931.

also shared this view. Zikowsky<sup>38</sup> expressed the belief that malignant neutropenia is a severe form of sepsis occurring in a weakened organism, resulting in injury to the granulopoietic tissue and paralysis of the organ complex (liver, spleen and endocrine glands), the secretions of which stimulate the bone marrow and regulate the entrance of the granular cells into the blood stream. He therefore believes that sepsis is the primary cause. Zadek<sup>39</sup> expressed the opinion that a virus of sufficient potency to destroy the granulopoietic tissue so completely could not uniformly spare all of the closely related contiguous cells. There are a number of observations which tend to eliminate the hypothesis of a septic or a toxic process acting on the myeloid tissue. The neutropenia may precede the appearance of local signs of infection,<sup>38</sup> or there may not be any demonstrable infection.<sup>40</sup> Also, the neutropenia may be definitely periodic, as in the case reported by Rutledge and his co-workers,<sup>41</sup> and in case 3 of Doan's series.<sup>19</sup> Biopsies<sup>2</sup> and post-mortem studies<sup>42</sup> of the marrow often show a peripheral neutropenia and leukopenia with myeloid hyperplasia.

*Hyperergic Inflammation.*—A few authors believe that benign and malignant neutropenia may be a form of hyperergic inflammation (allergy) in which the bone marrow is the point of least resistance. Schilling<sup>2</sup> has produced a blood picture similar to malignant neutropenia experimentally in anaphylaxis, so that he thinks it may be an anaphylactic condition instead of an individual disease. Bromberg and Murphy<sup>43</sup> reported a case following prophylactic vaccination against typhoid. Kracke<sup>44</sup> reported a case. He said: "The question of typhoid prophylaxis as a whole or partial cause of the condition must be considered." It is known that inactivated typhoid bacilli have a marked chemotactic effect on the bone marrow. Meyer<sup>45</sup> reported a case following malarial therapy. A few of the cases showing eosinophilia during the attack suggest anaphylaxis. These cases may have resulted from an overwhelming reaction to foreign protein in a sensitive subject.

38. Zikowsky, J.: *Wien. klin. Wchnschr.* **44**:203 (Feb. 6) 1931; 226 (Feb. 13); 259 (Feb. 20) 1931.

39. Zadek, I.: *Med. Klin.* **21**:694 (May 8) 1925.

40. (a) Author's case 4. (b) Hamburger, L. P.: *Bull. Johns Hopkins Hosp.* **48**:339, 1931.

41. Rutledge, B. H.; Hansen-Prüss, O. C., and Thayer, W. S.: *Bull. Johns Hopkins Hosp.* **46**:369 (June) 1930.

42. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: *Am. J. M. Sc.* **183**:104 (Jan.) 1932.

43. Bromberg, L., and Murphy, P.: *Agranulocytic Angina Following Prophylactic Typhoid Vaccination*, *J. A. M. A.* **92**:1266 (April 13) 1929.

44. Kracke, R. R.: *Am. J. Clin. Path.* **1**:385 (Sept.) 1931.

45. Meyer, A.: *Deutsche med. Wchnschr.* **57**:226 (Feb. 6) 1931.

*Congenital and Familial Anomaly.*—A familial tendency to diseases of the hematopoietic tissues of one type or another is a possibility. Hart<sup>46</sup> suggested a familial tendency, having observed malignant neutropenia in two sisters. Wolff<sup>47</sup> reported malignant neutropenia and myeloblastic leukemia as reactions to the same infection in a brother and sister. Bickel<sup>48</sup> said that congenital hematopoietic insufficiency is a possible explanation. Congenital granulopoietic insufficiency seems to have been proved in some cases, but the granulopoietic tissue in most of these patients had, so far as is known, functioned normally for many years. The cyclic and recurring nature of many cases is hard to explain on the basis of a congenital lesion. Blumer<sup>49</sup> dismissed the possibility of a congenital anomaly with the following statement: "The same patient has reacted with the usual leukocytosis and granulocytosis to one attack of an infection and has shown a neutropenic and leukopenic reaction to another attack." Whether certain patients have a constitutional and abnormal functionally limited bone marrow for making blood is as yet a theoretical question.

*Chemical Poisoning.*—Chemical poisoning of the granulocytic apparatus is possible, but usually drugs do not have an affinity for just the granulopoietic tissue. Farley<sup>50</sup> reviewed from the literature thirty-nine cases in which the function of the bone marrow was depressed following the use of various preparations of arsphenamine. The symptoms varied from those of purpura hemorrhagica to those of severe aplastic anemia and malignant neutropenia, depending on whether the principal effect was on the granulopoietic, megakaryopoietic or erythropoietic tissues, or on all of these combined. Since it is known that benzene is a powerful leukocytic depressant and taking into consideration the thirty-nine cases following the use of arsphenamine, it might be possible that any drug containing the benzene ring could be an etiologic factor, such as the many coal tar derivatives on the market which are used by the public indiscriminately. These drugs may serve to weaken the hematopoietic tissue. Benzene usually does not produce typical benign and malignant neutropenia, but a depression of all the bone marrow elements, so that anemia, purpura and sometimes methemoglobinemia, as well as leukopenia and neutropenia, are produced. Kracke<sup>51</sup> expressed the belief that benzene probably can be administered in such dosage as to produce marked granulopenia with no apparent effects on

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46. Hart, V. K.: *Laryngoscope* **37**:357 and 798, 1927.

47. Wolff, E.: *Folia haemat.* **44**:38 (April) 1931.

48. Bickel, L.: *Wien. klin. Wchnschr.* **42**:1186 (Sept. 12) 1929.

49. Blumer, G.: *Am. J. M. Sc.* **179**:11 (Jan.) 1930.

50. Farley, D. L.: *Am. J. M. Sc.* **179**:214 (Feb.) 1930.

51. Kracke, R. R.: *Am. J. Clin. Path.* **2**:11 (Jan.) 1932.

either erythrocytes or platelets. He has performed experiments on rabbits which bear out this point. In 1910, Selling<sup>52</sup> reported observations on three girls who had been working in a rubber factory and were suffering from benzene poisoning, characterized by "agranulocytosis" and complicated by purpura and hemorrhages. One of them had quit her work long before, illustrating the cumulative and delayed effect of the chemical on the hematopoietic tissues. This is a most important point to consider in connection with the coal tar products. Later, Selling<sup>53</sup> experimented with benzene as a leukotoxin. He injected benzene subcutaneously into rabbits, and demonstrated the production of leukopenia with little effect on the erythrocytes. Jacob and Douady<sup>54</sup> reported a case of malignant neutropenia in a patient treated with injections of gold sodium thiosulphate, showing the probable toxicity for the granulopoietic tissue of gold preparations. It has been known for some years that the granulopoietic tissues can be depressed with various chemicals, so that producing benign and malignant neutropenia experimentally with these agents is also attacking the problem, at least from an etiologic standpoint, from the wrong angle. Typical cases of primary neutropenia are not due to chemical poisoning.

*Paralysis of the Bone Marrow.*—Paralysis of the bone marrow, as expressed by some authors, cannot be considered at this time owing to the lack of knowledge concerning the regulation of the bone marrow by a nerve mechanism.

*Endogenous Disturbance of Production of Chemotactic and Maturation Factors.*—It is known that two different processes must be considered concerning the mechanism to maintain production and destruction of granulocytes at a constant level: (1) the mechanism of delivery of cells to the circulation and (2) the mechanism of maturation. It appears from reports on sternal biopsies<sup>3</sup> and on autopsies<sup>42</sup> that one or the other of these processes might be at fault independently in different cases. In typical cases of malignant neutropenia with myeloid aplasia, the part of the bone marrow that manufactures the granular leukocytes (level I, chart) has ceased to function, or nearly so. The life of the granular cells in the blood stream in normal conditions of health is considered to be from three to five days; therefore, when manufacture in level I ceases and the supply in levels II and III of the bone marrow is exhausted, the granulocytes of the blood stream would totally disappear in from three to five days after the exhaustion of levels II and

52. Selling, L.: Bull. Johns Hopkins Hosp. **21**:33, 1910.

53. Selling, L.: Bull. Johns Hopkins Hosp. **27**:83, 1916.

54. Jacob and Douady: Bull. et mém. Soc. méd. d. hôp. de Paris **54**:798 (May 19) 1930.

III. There is little evidence that the granulocytes are abnormally destroyed in the blood stream. The bulk of all evidence points to the fact that the primary lesion in these cases, so far as is known, is in the granulopoietic areas of the bone marrow, and that this condition precedes the clinical symptoms and local infections. What, then, accounts for the condition of the granulopoietic tissue? It seems reasonable to suppose that the primary lesion is not in the bone marrow but in the organ or tissue which gives rise to the substance (factor) that keeps maturation of the granulocytes regulated to a normal level or regulated so that destruction and production are kept constant. The textbook description of pernicious anemia can, with little alteration, be made to apply astonishingly well to this type of malignant neutropenia, the principal alteration being the substitution of the granulopoietic for the erythropoietic tissue. There may be remissions in both. Perhaps patients who appear to have fulminating cases of malignant neutropenia have had many attacks and remissions in the past. In each of these diseases there are lesions that one would expect following the depression of one or the other of the component parts of the marrow. It is easy to see how a great reduction of the granulocytes would be more rapidly fatal than a great reduction of erythrocytes. A maturation factor for erythrocytes has been found; it now remains to find a maturation factor for granulocytes. Chemical analysis of bacteria known to cause a sustained leukocytosis, owing to the fact that they supply both a chemotactic and a maturation factor, might lead to a solution. It seems more logical to search within the body for the specific organ extract regulating granulopoiesis. Animal experimentation, with the removal of different glands of internal secretion or the destruction of other tissues by various substances, with a careful check on the granulocytes, might lead to valuable information not only as to etiology but as to treatment.

The other group of cases showing peripheral neutropenia with slight hypoplasia, normal, moderate or marked hyperplasia of the myeloid tissue, may be considered as due to a lack of the chemotactic factor. The cells may be growing and maturing, but are not being called to the circulating blood. It is apparently in these cases that the patients recover spontaneously or are benefited by nucleotides. The normal stimulus for calling the granulocytes from the marrow to the circulating blood has been shown by experimental work<sup>55</sup> to be the liberated products (nucleic acid, adenine, guanine, etc.) from disintegrating granulocytes in the blood stream. This theory could account for the failures in the

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55. (a) Doan, Zerfas, Warren and Ames.<sup>18</sup> (b) Ames, Delano, and Huntley. A. A.: The Nature of the Leucocytosis Produced by Nucleinic Acid: A Preliminary Experimental Study. *J. A. M. A.* **29**:472 (Sept. 4) 1897. (c) Jackson, Henry, Jr.: *J. Biol. Chem.* **59**:529 (April) 1924.

treatment of patients with nucleotides, as clinically the cases were the same as those of the patients who recovered. If the maturation factor is absent, a chemotactic factor would be of little value.

#### PATHOLOGY

*Pathology of Lesions.*—The peculiar inflammatory reaction seen in lesions accompanying benign and malignant neutropenia is merely a consequence of the absence of circulating granular leukocytes. Tissue necrosis and ulceration, whenever they occur, present only the distinguishing feature of being unaccompanied by polymorphonuclear leukocytic infiltration. The cellular reaction that does occur is comprised mainly of lymphocytic infiltration and the appearance of endothelial leukocytes or macrophage cells. There is a lack of development of the protective inflammatory barrier to infection, which is the reason for the spread of such infection. The most common site for the development of focal regions of infection and necrosis is along various parts of the gastro-intestinal tract, particularly at those points where bacteria are normally abundant. It is possible that the lesions along the gastro-intestinal tract are affected by the usual bacterial inhabitants which gained the ascendancy as a result of the removal of the protective mechanism partially inherent in the normal function of the granular leukocytes.

*Pathologic Changes in the Bone Marrow.*—In practically all fatal cases the bone marrow is degenerated to a great extent, often liquid, and varies in color from red to straw. There may be areas of patchy necrosis in the marrow. Normoblasts and megakaryocytes are present usually in their normal numbers, but the myelocytes and polymorphonuclear cells are absent or nearly absent. There may be a few myeloblasts, some showing mitosis, but they are fewer than are present normally. In other cases, particularly with the maintenance of the gross fatty structure, granulocytes may be completely absent, or nearly so, but erythrocytes, lymphocytes and endothelial leukocytes are present. The latter two types apparently may be actually increased. The aplasia of the marrow involves the granulocytes only, and they are absent even under the oxydase reaction. In one fatal case reported by Fitz-Hugh and Krumbhaar<sup>42</sup> the bone marrow showed a myeloid hyperplasia. In Rosenthal's<sup>3</sup> benign cases of neutropenia, sternal biopsies disclosed a normal, light or marked myeloid hyperplasia. It is therefore apparent that two types of pathologic change underlie cases of neutropenia. In one type, maturation of granulocytes has ceased, and there are peripheral neutropenia and myeloid aplasia; in the other type, there is arrest of maturation with peripheral neutropenia and normal or hyperplastic myeloid tissue.

Hallermann<sup>56</sup> reported a case of malignant neutropenia which showed typical lymph follicles in the bone marrow. It is known that typical follicles are occasionally encountered in normal bone marrow, so that they probably did not have any connection with the disease in question.

*Infection of the Bone Marrow.*—Yellow marrow is at all times a potential reserve for blood formation, and there is some evidence that it may be a special factor of safety in infection. Müller,<sup>57</sup> in a series of cases of influenza, found that the red marrow had been invaded by organisms and damaged enough to cut down granulopoiesis, while the yellow marrow had escaped infection and was becoming active. It will be remembered that influenza is characterized by leukopenia. Müller,<sup>58</sup> in another article, reported the vertebral marrow involved in more than 80 per cent of a series of different infections and the marrow of the long bones in only 25 per cent. Infection of the bone marrow in benign and malignant neutropenia has never been demonstrated except in terminal septicemia. The work along this line, however, has not been exhaustive, and further research may show this to be a great factor, especially in fulminating cases. Infection could take place quickly in a marrow devoid of granulocytes, and prevent the resumption of granulopoiesis.

*Pneumonia in Malignant Neutropenia.*—When pneumonia occurs, it is characterized by the appearance of a diffuse edema. The gross picture is similar to that of influenzal pneumonia if death occurs during the neutropenia. Subpleural hemorrhages are frequently observed. Microscopically, there is no evidence of pneumonia, but a diffuse acute hemorrhagic edema with little phagocytosis and no signs of inflammation.

*Pathologic Changes in the Spleen.*—The reaction in the spleen was found to depend on the predominance of toxic or septic symptoms. In cases observed at autopsy, a splenic tumor, partly of splenic character, was disclosed in some cases. Enlargement of the spleen in some cases has been found to be due to a great increase in the reticulo-endothelial cells, which outnumber the lymphoid cells. The lymph follicles are not prominent on the cut surface. Microscopically, the sinuses are filled with erythrocytes, proliferating reticulo-endothelial cells and lymphoid cells. Oxydase-positive cells are absent or scanty. The lymph follicles are small and atrophic, and there are no young cells or lymphoblasts in the germinal centers, only mature lymphocytes. Small anemic infarcts are occasionally seen.

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56. Hallermann, W.: *Folia haemat.* **42**:1 (Aug.) 1930.

57. Müller, E. F.: *Ztschr. f. Hyg. u. Infektionskr.* **93**:223, 1921.

58. Müller, E. F.: *Virchows Arch. f. path. Anat.* **246**:49, 1923.



*Pathologic Changes in the Liver.*—The liver may be somewhat enlarged and show cloudy swelling. Microscopically, some cases have shown fatty degeneration, and occasionally small multiple foci of necrosis. There is an increase in Kupffer's cells. There are bile casts in the bile capillaries and bile pigment in the hepatic cells. Sometimes there are interstitial lymphatic infiltrations.

*Pathologic Changes in the Lymph Nodes.*—The pathologic changes in the lymph nodes as given by Hueper and Garrison<sup>20</sup> are as follows: The submaxillary, cervical, peribronchial and mesenteric lymph nodes are in general enlarged, and they sometimes contain hemorrhages. Microscopic examination reveals atrophy of the lymph follicles; there are no young lymphocytes in the germinal centers, only mature lymphocytes being present. There is a proliferation of the reticulo-endothelial cells.

#### LABORATORY DATA

The results of laboratory examinations in this disease are of the greatest importance, since without following the total leukocyte count, as well as the differential count, at frequent intervals, an accurate diagnosis cannot be made and the progress of the disease followed. It is necessary to distinguish this syndrome from a number of other diseases characterized, in part, by low total leukocyte counts as well as by lymphocytosis. As a rule, this is not difficult and can be done easily on a basis of results of clinical and laboratory examinations. It is probable that many cases with characteristics of malignant neutropenia are overlooked because of inadequate laboratory studies. For comparable results, counts should be made in these cases at the same hours each day; thereby cognizance is taken of the rhythmic delivery of granulocytes to the blood stream. Daily leukocyte and differential counts are essential in following the results in any form of treatment. In some cases it is well to make two or three examinations in the twenty-four hour period.

*Total Leukocytes.*—One of the outstanding laboratory findings in this disease is, of course, the marked leukopenia. In a severe, fulminating case the total leukocytes may be so low as to be practically uncountable. It is necessary in these low counts to use a 1:10 dilution of the blood instead of the usual 1:20, and greater accuracy may be had by using the Fuchs-Rosenthal counting chamber, which gives a depth of 0.2 mm. Several square millimeters should be counted and an average taken. In the mild cases with a relatively slow course, the number of total white cells may be quite normal at first, but may gradually fall to 1,000 or less per cubic millimeter. The entire drop in the leukocyte count at the beginning of the disease is due to the disappearance of granulocytes. In fulminating cases, when first seen, the total leukocyte

count may be 700 or 600. In some cases the counts are reported as low as 200 total white cells. In practically all cases the counts are below 2,000.

*Granular Leukocytes.*—The second most outstanding laboratory finding in this disease is the neutropenia. The neutrophilic granulocytes may range from around 40 or 30 per cent in the most chronic and less severe cases to a total absence in the fulminating cases. One striking feature is that their morphology, in practically all cases, is normal. Complete studies on the changing differential counts of the white blood cells have been made in but relatively few of the reports recorded in the literature, chiefly, it is presumed, because of the rapid course of the disease, and secondly, because of the extreme leukopenia, which makes finding of the cells difficult. Dameshek and Ingall<sup>37</sup> reported in one case the gradual disappearance of granulocytes, most of which were immature forms. A terminal rise in immature granulocytes has been commented on by Krumbhaar,<sup>59</sup> who, observing this phenomena in fatal cases of mustard gas poisoning associated with marked leukopenia, called it a "myelocytic crisis." Schilling<sup>2</sup> explained its mechanism thus: The toxic or infectious agent destroys most of the granulopoietic tissue; the remaining granulocytes, however immature, gradually or suddenly appear in the blood stream, until finally the available stock of granulocytes becomes totally exhausted, the total count gradually decreasing during this time. Schilling called this a "degenerative shift." In most of the fatal cases of this disease, the maturation factor is absent, but the chemotactic factor is present, causing the granulocytes to continue being delivered to the circulation until the supply is exhausted. These are the cases showing myeloid aplasia. The amount of the chemotactic factor could determine the rate of delivery. In cases of "maturation arrest," the normal supply or an oversupply of granulocytes is in the hematopoietic tissue, but a chemotactic factor to call them to the circulation is absent. In these cases, when a chemotactic factor is supplied, mature cells are ready to be delivered to the circulation and few young forms are seen. These observations make it impossible to say at times, from the appearance of the blood slide alone, whether the patient is recovering or whether there is just an "agonal" outpouring of the remaining young cells. The total count in conjunction with the differential count aids in making the decision. The data on stab or rod forms in this disease are meager. In two of the four cases reported by Friedemann,<sup>60</sup> the finding of rod or stab nuclears is recorded. In one case, two days after the first roentgen treatment and four hours after

59. Krumbhaar, E. B.: J. M. Research **40**:497, 1919; Rôle of the Blood and the Bone Marrow in Certain Forms of Gas Poisoning: I. Peripheral Blood Changes and Their Significance, J. A. M. A. **72**:39 (Jan. 4) 1919.

60. Friedemann, U.: Deutsche med. Wchnschr. **53**:2193 (Dec. 23) 1927.

the second, there were 34 per cent. In the other case, they ranged from 2 to 7 per cent during recovery.

In practically all of the cases reported in the literature, the eosinophils were either absent or present in normal or slightly increased percentage. In all of the cases to be reported, they were absent during the attack. The basophils are either absent or in normal percentage.

*Viability of Granulocytes.*—Rutledge and his associates<sup>41</sup> studied the viability of the granulocytes in a case of cyclic benign neutropenia by supravital staining. They found that just before and during an attack the motility of the neutrophilic granulocytes became much reduced, and their vitality, as well as their capacity to take the neutral red dye, was much diminished. Their viability was frequently no more than half of the normally expected time of life, and their motility between attacks never approached normal. The eosinophils during this time (they were always increased during an attack in this patient) showed, on the contrary, great motility and increased viability.

*Lymphocytes.*—The lymphocytes may at first be present in their normal absolute numbers, the entire drop in the total leukocyte count being due to the disappearance of neutrophilic granulocytes. As the disease becomes more and more severe there is a relative increase, but in most instances an absolute decrease, of lymphocytes. They may become greatly reduced. The morphologic characteristics of all the lymphocytes are, as a rule, perfectly normal. With a total normal count of 6,000, there are in the blood stream from 21 to 25 per cent lymphocytes and from 4 to 8 per cent endothelial leukocytes; which means, combining the two, that there are from 1,500 to 1,980 nongranular white cells per cubic millimeter in the circulating blood under normal conditions. Therefore, when the total number of cells in malignant neutropenia reaches from 1,980 to 1,500 per cubic millimeter, if there is 1 per cent or more granular cells, the lymphocytes and endothelial leukocytes are being reduced in their absolute numbers. The percentage of reduction can be determined roughly by the percentage of granular cells present after the total count has been lowered to the foregoing figures. With a total count of 1,000 or less, the absolute number of lymphocytes is greatly reduced. The mechanism of the reduction in lymphocytes is obscure, as there is no evidence of the destruction of lymphoid tissue. Only theories can be advanced. If the pathologic changes in the lymph nodes as reported by Hueper and Garrison<sup>29</sup> are present in all cases, they may account for the diminution of lymphocytes.

*Endothelial Leukocytes (Monocytes and Transitionals).*—These may at first be present in their normal absolute numbers. As the disease becomes more and more severe, there seems to be a depression in reticulo-endothelial tissue, so that the absolute number of endothelial leukocytes becomes much reduced. Some authors report an absolute

increase in endothelial leukocytes at the beginning or during recovery in a case and consider it due to a marked proliferation of the reticulo-endothelial system, particularly in the spleen. Schilling<sup>2</sup> stated that in malignant neutropenia the endothelial leukocytes (monocytes) are greatly increased in contrast to the neutrophils. On the other hand, many authors do not accept as malignant neutropenia any case in which there is a significant absolute increase in either lymphocytes or endothelial leukocytes. When present in normal numbers, their morphology seems to be normal. Conner and his associates<sup>61</sup> reported an increase in the percentage of endothelial leukocytes in three of five patients. Goldenberg<sup>62</sup> reported the case of a patient with two attacks, death occurring in the second. The endothelial leukocytes were highest during the second attack. He said: "This increase of endothelial leukocytes may be interpreted as an extra medullar effort to meet the emergency." The cells, being macrophages, may be interpreted as coming to take up the work of the absent granulocytes. Ferrata<sup>63</sup> said that the cell known as the clasmatoocyte, macrophage or reticulo-endothelial type, may elaborate specific granulations in its cytoplasm and become a granulocyte. He found such cells in the blood stream, containing either neutrophilic or eosinophilic granulations, and termed them "hemohistiocytes." If one accepts this theory of Ferrata, then Goldenberg's assumption concerning the increase of these cells is correct. Doan and Sabin<sup>64</sup> have offered another explanation for the "hemohistiocytes," namely, that neutrophilic and eosinophilic granules may be phagocytosed from granulocytes and their débris. Since there is such a scarcity of material to phagocytose in the final stages of this disease, this explanation does not seem to apply.

*Türk's Irritation Forms.*—There is not any information to be found in the literature concerning these cells in cases of benign and malignant neutropenia. As they appeared in cases of my series, it might be well to include some information concerning them. Schilling<sup>2</sup> said: "They originate partly from the migratory cells of the tissues; they may be found in normal blood at times especially during acute irritations of the marrow or of the lymphatic organs through anemias and leukocytoses; . . . they may be merely functional types of lymphocytes or myeloblasts." In one of my cases, they appeared on the fifth day before death and increased to 11 per cent in the last count made a few hours before death. In another case, the cells ranged from 1 to 7 per cent during the first eight days while the patient was in the acute stage of her illness.

61. Conner, H. M.; Margolis, H. M.; Birkeland, I. W., and Sharp, J. E.: *Proc. Staff Meet., Mayo Clin.* **6**:193, 1931.

62. Goldenberg, C.: *Virginia M. Monthly* **58**:391, 1931.

63. Ferrata, A.: *Le emopatie*, Milan, Italy, Società editrice libraria, 1918, vol. 1.

64. Doan, C. A., and Sabin, F. R.: *J. Exper. Med.* **44**:285, 1926.

They were absent during the last five days before discharge from the hospital. In the other cases, they ranged from 1 to 2 per cent. According to the literature, these cells signify only an acute irritation of the bone marrow.

*Erythrocytes.*—In typical cases the erythrocytes are not affected. If, however, the illness lasts more than the usual ten days, the erythrocytes may be affected and diminished. In fulminating cases the erythrocytes are not affected because there is not time. The erythrocytes and hemoglobin may have been low before the attack, in which case the decrease cannot be said to be due to the neutropenia. This was noted in one of my cases which occurred during the seventh month of gestation, at which time anemia is often found. When anemia is present, it is of the secondary type with erythrocytes more or less achromic and their average diameter less than 7 microns.

*Blood Platelets.*—Most authors are agreed as to the normal or the increased numbers of blood platelets. They may become reduced if the disease is of fairly long duration and the bone marrow becomes more or less aplastic, but ordinarily the patient dies before this eventuality occurs. In malignant neutropenia (secondary) due to benzene and other drugs the blood platelets are reduced.

*Toxicity of the Serum.*—Hansen-Prüss<sup>41</sup> carried out studies on the toxicity of the serum in a case of cyclic benign neutropenia. During and before an attack, normal leukocytes of the same blood group mixed with the patient's serum lost their motility and became rounded in forty-five minutes, while several of the previously active motile granulocytes were dissolved. This same serum had no influence on washed lymphocytes or endothelial leukocytes. In a control mixture of type two serum and homologous washed leukocytes, the granulocytes retained their motility for an hour and a half. Hansen-Prüss regrets that he was not able to carry this experimental work as far as he wished so as to prove or disprove the point. Roberts and Kracke<sup>24</sup> performed the following experiment to determine the toxicity of the serum: When their patient's white cells totaled 400, they took 2 cc. of the patient's blood (oxalated) and mixed it with 2 cc. of normal blood of the same type. Two cubic centimeters of normal oxalated blood was mixed with 2 cc. of another normal blood for control. Differential and total white counts were made at two hour intervals for forty-eight hours, but neutrophilic destruction could not be demonstrated. This experiment would demonstrate only the presence of granulocytes, but would not determine if their motility had been destroyed, or whether or not the cells were viable. It is known that some normal serums will be incompatible, that is, will possess specific leukotoxins for the granulocytes of another patient belonging to the same group, and that when oxalate or

citrate is added, the plasma is doubly toxic. Experiments on leukotoxins by Doan<sup>65</sup> show that this factor must be taken into consideration in any experiment to determine the toxicity of the serum. Conner and his co-workers<sup>61</sup> supported the destructive theory of the blood serum in this disease with the fact that in one of their cases, three hours after transfusion there were 300 less white cells. This is not conclusive evidence either, as the limit of error in counting cells (200) is known, and the rhythmic delivery of cells to the blood stream must be taken into consideration. One can, therefore, say that sufficient proof is not at hand concerning the toxicity of the serum in malignant neutropenia.

*Blood Cultures.*—Many cases have shown positive blood cultures, *Streptococcus viridans* and *haemolyticus*, *Staphylococcus aureus*, *Pneumococcus*, *Bacillus coli* and *Bacillus pyocyaneus* being most frequently found. These blood cultures have not been sufficiently ignored, especially if they occur late in the disease, since the disease is characterized by an early breaking down of the normal protective mechanism. Many cases have had negative blood cultures.

*Urine.*—The urine in malignant neutropenia is not significant. There may be albumin and casts in varying amounts. The urinary findings would be those expected in any febrile disease.

*Cultures and Direct Smears from the Throat and Mouth.*—Direct smears from lesions of the mouth many times show *Borrelia vincenti* (Vincent's organisms), *Fusiformis dentium*, streptococci, pneumococci and staphylococci. All of these organisms, except Vincent's organisms, appear in the routine cultures. All of these organisms make their appearance sooner or later in most lesions of the mouth, especially in those associated with diseases of the blood. The organisms and their lesions may be considered incidental and secondary. Mucous membranes are normally protected by the granulocytes, which can be found in abundance in these areas. When this normal protective barrier is removed, lesions can be expected, as organisms are always present.

*Biopsies on Specimens of Bone Marrow.*—These are important in enabling one to study the mechanism of malignant neutropenia while the patient is still alive. Furthermore, biopsy on the fresh specimen of bone marrow is immeasurably superior to the specimen observed at autopsy, even if postmortem examination is done within a few hours after death. Biopsy on the sternal bone marrow is the method par excellence for the exact differentiation between neutropenia with a maturation arrest (normal myeloid tissue, light or marked myeloid hyperplasia), neutropenia with myeloid aplasia and certain other diseases affecting the bone marrow.

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65. Doan, C. A.: The Recognition of a Biologic Differentiation in the White Blood Cells, J. A. M. A. **86**:1593 (May 22) 1926.

## SYMPTOMS

The patients are wilted in appearance; the skin is pale, but the mucous membranes are of good color. The weakness, marked prostration and toxic appearance are out of all proportion to the few physical signs. Jaundice is rare in typical cases. The liver and spleen may be enlarged. The patients are characterized by weakness, easy fatigue, drowsiness and tendency to infection, especially in the oral cavity. There is evidence that just mere lack of neutrophils will cause such symptoms as fever, weakness, inertia and mental and physical collapse. Roberts and Kracke<sup>28</sup> were among the first to recognize the importance of analyzing accumulated data in reference to the white cell level and the symptomatology. They found that complaints of weakness, exhaustion and fatigue were twice as frequent in the neutropenic patients as in those showing a normal white cell count. Furthermore, the severity of the symptoms paralleled to a remarkable extent the degree of neutropenia found. The fulminating cases are rapid in progress, with a comatose condition usually preceding death. The disease may last from three days to three months, in rare cases a number of years, and end with death or with recovery. The benign cases usually correspond to the fatal group of cases as far as the early symptoms are concerned.

*Onset.*—Fever, chill and sore throat are the usual mode of onset, which may be sudden or gradual. There may be added to these headache, marked palpitation with a tumultuous heart beat, general aching, drowsiness and occasionally delirium. Some patients are nauseated and vomit, and, as a rule, there is dysphagia. There is an offensive, fetid odor to the breath, and the tongue is often heavily coated. According to Roberts and Kracke,<sup>24</sup> there are three onsets: a marrow onset, a blood stream onset and a clinical onset. There is another type with a blood stream onset and a clinical onset, the marrow being normal or hyperplastic.

*Fever.*—The temperature ranges from 101 to 106 F. and is of the continual type. In mild or chronic cases, the temperature may be normal or only slightly elevated.

*Previous Health.*—A great many patients give a history of weakness or lack of vitality for varying periods before the onset of the condition, especially in the chronic recurring cases. Some patients state that there was a lack of energy for years and a marked weakness for a few weeks or months before the onset of the acute symptoms. On the other hand, neutropenia occurs in some patients who have always been well and who were active physically and mentally until the sudden onset. These cases are more rare, and it may be that an undetected chronic granulopenia had been present. Occasionally, benign and malignant neutropenia follow in wake of some other disease.

*Angina.*—It cannot be said that the relationship between neutropenia and stomatitis is quantitative, but it is known that a severe leukopenia, especially a neutropenia, is frequently associated with lesions of the mouth, probably because the oral cavity constantly harbors virulent organisms and its natural barriers are subjected to frequent insults. All patients do not have lesions of the mouth. The unusually good oral hygiene practiced by some patients probably accounts for this.

*Local Lesions.*—The local lesions seen in benign and malignant neutropenia usually occur on the mucous membranes, more rarely on the skin. Lesions of the mucous membranes when present, are localized mainly in the mouth and involve various structures, such as the gums, tonsils, soft palate, lips, pharynx and buccal mucous surface. More rarely the nose, uterus, vagina, rectum, anus and skin are involved. Local lesions may also occur any place along the gastro-intestinal tract or in the lungs, and the symptoms are according to the areas involved. There may be regional adenopathy with necrosis and sloughing of the overlying tissues and skin. The tonsils, when involved, have in some cases sloughed away.

*Character of the Local Lesions.*—The local lesions may be inflammatory, with marked edema, ulceromembranous or gangrenous. The areas may slough, and there may be severe hemorrhage from them. The membrane, when present, may be dirty yellow, gray or greenish black.

*Clinical Types.*—1. Fulminating, acute type, like the cases originally reported by Schultz.<sup>9</sup> The onset is sudden, with a chill, high fever and necrotizing angina; occasionally there may be jaundice, and albuminuria is frequently present. The blood shows an extreme degree of leukopenia and neutropenia, and the bone marrow reveals a widespread necrosis of the granulopoietic system. This type is rapidly fatal. 2. Subacute type, in which the illness is more prolonged. Thompson<sup>66</sup> reported a series of these cases with the following clinical picture: There are several days of fever, followed by a moderate, soft, tender enlargement of the lymph nodes and spleen, accompanied by moderate to extreme leukopenia and a reduction in neutrophils, often reaching an almost complete absence. There is a relative increase in the endothelial leukocytes, and abnormal forms are sometimes seen. Toward the end of the disease the pharynx becomes red and sore, and scattered, round, superficial, whitish spots appear on the posterior pharyngeal wall. The disease lasts from one to three weeks, and with but one possible exception in his series, all of the patients recovered promptly and completely, almost by crisis. 3. Recurring, or relapsing cases. Patients with this type have two, three or more attacks several weeks or months apart. The symptoms during an attack may be similar to those in the

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66. Thompson, W. P.: Am. J. M. Sc. 180:232 (Aug.) 1930.



fulminating or subacute types. Death may occur in the second or third attack; the patients may make a complete recovery, or the process may become subchronic. 4. The subchronic type. In this type the cases begin insidiously. The leukopenia usually is less intense, and the number of granulocytes is higher than in the other types. Some show a high percentage of endothelial leukocytes. There is necrosis of the bone marrow, but it shows an active power of regeneration. The patients may be sick for a year or more and finally recover. Rosenthal<sup>3</sup> reported two subchronic cases in his series which had been under observation for six years. They showed a continuous leukopenia of 1,500 without symptoms, except easy fatigue. 5. Cyclic type. These cases present a chronic, regularly recurring, periodic neutropenia. Only two cases of this type are reported. One of the patients<sup>41</sup> had an attack of neutropenia every three weeks, beginning in 1910, when he was 2½ months old, and these attacks still continued when he was last observed in 1930. The other patient (case 3<sup>19</sup>), a woman, aged 18, has been studied over a period of more than a year. There recurs in this patient, on the average of from every twenty to twenty-one days, a relative and absolute neutropenia of severe grade, without the appearance of immature cells in the blood and uninfluenced by the administration of pentose nucleotide. This cycle is unassociated with the menstrual history. Occasionally, the five types may be mixed, as subchronic recurring or subacute recurring. These varying types and the degree of severity of the neutropenia may depend on the type and degree of reduction of the maturation factor or the chemotactic factor for granulocytes.

In many patients suffering from an attack of benign or malignant neutropenia pneumonia has developed, and in some typhoid fever. It may have been that the typhoid organisms were in the intestinal tract and the pneumococci in the throat, as in carriers, and as the neutropenia developed, these organisms invaded the unprotected tissues, giving an associated, or secondary, independent infection.

#### DIAGNOSIS

Neutropenia must be diagnosed early if the mortality is to be reduced. There should be more critical cytologic examinations of the blood, as there is much evidence in the literature that the neutropenia precedes all other symptoms. To wait for the appearance of sore mouth, sore throat, fever and prostration is only giving the army of organisms time for invasion. The patient is ill from several days to several weeks, or perhaps months, before the acute stage in many cases. The history of some cases shows that the patients were treated for a week or more for influenza, sore throat or diphtheria. Diagnosis in a typical case is fairly easy. The symptoms and blood picture are as characteristic as those occurring in pernicious anemia. A typical history is the appear-

ance of sore throat in a middle-aged patient, usually debilitated, accompanied by chills and fever, ulceration and then membrane formation in the throat and on the buccal mucous membrane. If angina is absent, with only fever of more or less long duration and with but few clinical signs, the diagnosis is more difficult. The rule should be to follow up each case of continued fever with frequent leukocyte and differential counts. If angina and fever are both absent and there are only weakness, malaise and drowsiness, a frequent leukocyte and differential count should be made. Since many cases are reported to have followed Vincent's angina and trench mouth, a careful study of the blood should be made in these cases. Other cases have been reported following the extraction of teeth and tonsillectomy, so that a total leukocyte and differential count should precede these operations. The diagnosis is made on the low total count and the neutropenia. Some authors state that normal numbers of circulating erythrocytes and thrombocytes are essential to the diagnosis and do not accept as malignant neutropenia any case in which there is a significant absolute increase in lymphocytes or endothelial leukocytes. A sternal marrow biopsy would aid in the diagnosis and distinguish the aplastic from the hyperplastic type.

#### DIFFERENTIAL DIAGNOSIS

Acute follicular tonsillitis, Vincent's angina and diphtheria are to be differentiated by appropriate clinical means and a routine leukocyte and differential count. None of the aforementioned disorders causes leukopenia. Gordon and Litvak<sup>67</sup> discussed the differential diagnosis between diphtheria and oral lesions of the blood dyscrasias. Patients with streptococcic sore throat with *Streptococcus haemolyticus* septicemia occasionally have leukopenia, but rarely less than 5,000 or 4,000 cells, and the differential count usually shows at least 85 per cent neutrophils. In typhoid fever and influenza the total white cell count is rarely less than 4,000, and the neutrophilic percentage is at least 25. Generalized, rapidly advancing tuberculosis may show a marked leukopenia, as low as 3,000 cells, but the neutrophils comprise from 90 to 99 per cent, mostly immature forms. Pneumonia may at times cause leukopenia, rarely below 6,000 cells, and there is always a preponderance of neutrophils. Benign and malignant neutropenia without angina may simulate any febrile disorder associated with leukopenia. A frequent leukocyte and differential count should be made until the diagnosis is established.

*Lymphosarcoma.*—This condition may cause leukopenia with a reduction in neutrophils. The clinical course will serve to make the diagnosis, and it may be confirmed by the biopsy findings.

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67. Gordon, M. B., and Litvak, A. M.: *M. J. & Rec.* **131**:35 (Jan. 1); 74 (Jan. 15) 1930.

*Leukemias.*—Benign and malignant neutropenia can be differentiated from lymphatic reactions by the fact that in lymphatic reactions there is an absolute increase in lymphocytes, which replace the neutrophils to make the total leukocyte count normal or increased. The lymphatic reactions there are usually many abnormal lymphoid cells, while in benign and malignant neutropenia most of the lymphocytes are normal. The differential diagnosis between acute leukopenic lymphatic leukemia and malignant neutropenia may be so difficult as to be well nigh impossible. In rapidly developing acute leukemia the leukocytes may fall as low as 1,200 or 2,000. The biopsy on the bone marrow will establish the diagnosis in doubtful cases. In the leukemias there is a crowding of the marrow with lymphoid cells. Chronic leukemia with low values for leukocytes also must be ruled out.

*Aplastic Anemias.*—In aplastic anemia, the onset of the fever is usually not so abrupt and there are subcutaneous hemorrhages and hemorrhages from mucous membranes. There is aplasia of the bone marrow as a whole, resulting in a yellow marrow which is completely barren of erythrocytes, leukocytes and megakaryocytes. There are leukopenia, neutropenia, thrombocytopenia and rapidly advancing anemia of the hyperchromic type. The color index is irregular. There is a relative increase in lymphocytes. If anemia is present in benign or malignant neutropenia, it is of the secondary type; the erythrocytes are more or less achromic, and their average diameter is less than 7 microns.

*Infectious Mononucleosis.*—In this disease there occasionally may be seen low values for leukocytes. In this condition, the injection of foreign protein will result in an increase in the circulating neutrophils. The clinical manifestations are usually much less severe than in benign and malignant neutropenia.

Care must be taken, also, to distinguish pernicious anemia in an aplastic phase and metastasis to the bones producing the so-called myelophthisic anemia.

Careful inquiry should be made, also, regarding intoxication from benzene, the administration of arsenicals, especially those of the arsphenamine group, and the use of the roentgen rays, radium and thorium X.

#### PROGNOSIS

In the beginning, the mortality was reported as 100 per cent. Kastlin,<sup>68</sup> in 1927, reported a mortality of 95 per cent. Friedemann,<sup>69</sup> in 1927, gave the mortality as 92 per cent. Harkins,<sup>69</sup> in 1931, reviewed the literature and stated that up to the date of writing at least one

68. Kastlin, G. J.: *Am. J. M. Sc.* **173**:799 (June) 1927.

69. Harkins, H. M.: *Granulocytopenia and Agranulocytic Angina with Recovery*, *Arch. Int. Med.* **47**:408 (March) 1931.

hundred and fifty cases with twenty-seven recoveries had been reported, the approximate mortality rate being 82 per cent. In 1931, Rosenthal<sup>3</sup> reported a series of twenty-six cases, twelve of fatal malignant neutropenia and fourteen of benign neutropenia, giving a mortality of 46.2 per cent in his series. Many of the fourteen patients who recovered had been under observation for six years. Taussig and Schnoebelen<sup>69a</sup> in a review of three hundred and twenty-eight cases (which included the so-called secondary types), found that the mortality was 75 per cent without special therapy and with miscellaneous forms of treatment; 63 per cent with transfusions of blood, and 53 per cent with roentgen treatment. Jackson and his co-workers<sup>69b</sup> reported a mortality of 30 per cent in fifty-four typical cases of agranulocytic angina in which treatment consisted of nucleotides. It will be seen that since 1927 the reported mortality rate has steadily decreased. The increasing use of blood counts will probably cause the reported mortality rate to continue to decrease. Fulminating cases are rapidly fatal, while recoveries are to be expected in those cases which are more prolonged and milder. Very few patients recover if the total count falls below 1,000. Kracke<sup>44</sup> reported one case in which the leukocytes fell as low as 470 and the patient recovered, only to die in a second attack. Friedemann<sup>60</sup> and others ascribed their recoveries to roentgen treatment. Wyatt<sup>70</sup> reported one case in which the patient recovered after surgical drainage of multiple abscesses. Paroulak<sup>71</sup> reported one case with recovery after repeated transfusions. Many recoveries are reported following nucleotide therapy, the mortality with this form of treatment being the lowest. A great many patients are reported to have recovered without any active treatment. Recoveries and deaths are reported with all forms of treatment. It can be seen that the reduction in mortality cannot be ascribed solely to any one mode of treatment. It seems more probable that the reduction is due to the recognition of more cases, owing to more critical studies of the blood and thereby the inclusion of the more chronic cases in the group. Many authors consider that an absolute increase in endothelial leukocytes has some relationship to the severity of the disease and its prognosis, but there is insufficient evidence in the material collected from reported cases to make this a certainty. In the early stages of the disease, the outcome cannot be determined, as in the cases showing myeloid aplasia it depends entirely on whether maturation of the granulocytes will be resumed. In the

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69a. Taussig, A. E., and Schnoebelen, P. C.: Roentgen Treatment of Agranulocytosis, *J. A. M. A.* **97**:1757 (Dec. 12) 1931.

69b. Jackson, H., Jr.; Parker, F., and Rinehart, J. F.: *Am. J. M. Sc.* **184**:297, 1932.

70. Wyatt, T. C.: *New England J. Med.* **199**:525, 1928.

71. Paroulak, J.: *Arch. d. mal. du cœur* **20**:648, 1922.

cases showing peripheral neutropenia and normal or hyperplastic myeloid tissue, the outcome depends on the resumption of delivery of the cells to the circulation.

#### TREATMENT

A review of the literature indicates that most authors believe that a specific and satisfactory treatment has not yet been discovered for neutropenia, many believing that recovery, when it does take place, is spontaneous and not influenced by the type of treatment. Many cases are on record in which spontaneous recovery took place in what seemed in the beginning to be a malignant (fatal) case. Such a case was reported by Hamburger,<sup>40b</sup> in a patient with 1,500 white cells and 2 per cent neutrophils. There was a gangrenous area over the most prominent part of a left lateral cervical glandular swelling which sloughed. This patient recovered in four weeks without any active treatment, and was still well five years later. One patient who came under my observation recovered without any active treatment except rest and a diet rich in vitamin B. Also, in many cases in which recovery occurred several types of treatment were used, so that it was impossible to draw decisive conclusions as to the efficacy of the measures that were used, or to say which, if any, was responsible for the cure.

The treatment for this disease must be considered under two headings. First, treatment in the acute cases, which means the employment of an agent that will stimulate maturation of the granulocytes and cause their delivery to the circulating blood in the shortest time possible. The mere absence of granulocytes from the blood stream for seven days is probably incompatible with life, and in a system devoid of granulocytes infection quickly takes place. Second, one must consider the treatment of patients with chronic cases with the object of preventing a recurrence if possible.

*Treatment for Local Lesions.*—Neutropenia is characterized by an early breaking down of the normal protective mechanism afforded by the neutrophilic granulocytes. With these granulocytes absent, the organisms ever present in and on the body quickly invade. Therefore, infection, local or general, is the most frequent complication of benign and malignant neutropenia. The most frequent local lesions are in the mouth and throat. An antiseptic that will not cause a chemical destruction of the tissue is advised. For local treatment to the oropharyngeal lesions, Hamburger<sup>40b</sup> advised the following: After nourishment, the mouth and throat are sprayed with a saturated solution of potassium chlorate, a compressed air atomizer being used. Following the spraying, each ulcerated area and the gums are swabbed with a solution of copper sulphate, 10 grains (0.65 Gm.) to the ounce. This oral treatment is given as often as five times a day, and less frequently as improvement takes place.

Phlegmonous masses in any locality should not be incised unless absolutely necessary, since no local abscess forms under the existing granulopenic state. After the neutrophilic granulocytes return to the blood stream in sufficient numbers, abscesses may form, and incision and drainage may be instituted if necessary. However, when the neutrophilic granulocytes return, many pathologic conditions will right themselves. Surgical procedures of any type should not be attempted for these patients, as it is dangerous in the presence of a leukopenia, especially a neutropenia. Such a procedure may bring about a sloughing of tissue, as healing cannot take place normally in the presence of a leukopenia and neutropenia. There are cases on record in which necrotizing changes have appeared in the skin at the site of venipuncture.

*Miscellaneous Agents Used.*—In the past it was thought that an agent introduced subcutaneously which would cause a local abscess would in this way stimulate the production of neutrophilic granulocytes. Turpentine was used for this purpose. Intramuscular injections of milk were given for the foreign protein reaction. Such agents are rarely used now, as they have not been shown to have any therapeutic value. Intravenous injections of gentian violet and acriflavine have been given, but they will not stimulate the production of granulocytes. Perhaps they were used with the idea in mind that there was an infection of the blood stream. Fetal liver and extract of bone marrow have been administered, but no definite results have been attributed to them. Squibbs leukocytic extract, in daily intramuscular injections of 50 cc., divided into two doses, has been used in many cases along with transfusions and other forms of therapy. Definite and gratifying results from the aforementioned agents were lacking, and they are rarely used now.

*Preventive Treatment.*—There is little definite information available as to the management of chronic cases and the prevention of recurrence of acute attacks. Roberts and Kracke<sup>20</sup> made a statistical study of eight thousand records of leukocyte and differential counts from a series of ambulatory patients seen between 1920 and 1930. Their study points out many interesting facts. In the granulopenic group of this series, the count ranged from 4,000 down to 1,000. There were one thousand eight hundred and eighty-one patients with a granulopenia, or one of every four. This number is significant, since benign and malignant neutropenia develop chiefly in patients with granulopenia. In this group the chief complaint was weakness. The evidence accumulated indicates that weakness, exhaustion, fatigue and tendency to sleep are the chief results of a depressed granulocyte count. Patients who have had more than one or two attacks know by their feelings when granulopenia is present. A great many patients give a history of great mental stress or emotional shock. A number of patients with chronic cases improve with rest. Roberts and Kracke, in their series, reported two

such cases; one patient, a man, improved during 1931, business being so poor he had rested more than usual; the other, a physician, improved after retirement, but the condition left him with a loss of 30 pounds (13.6 Kg.) that he never regained and myocarditis. Just in what manner the granulopenia affects the heart is not clear, but arrhythmia, tachycardia and tumultus heart beat are recorded in many cases. This makes it appear essential that patients with granulopenia rest in bed until the granulocytes approach normal. From the foregoing, then, it can be said that rest and freedom from mental and emotional stress should be advised. It would also seem advisable that such patients should refrain from using any drugs shown to have a depressing effect on the granulopoietic tissue, such as those containing the benzene ring. It would be advisable, also, to attempt to clear up all foci of infection, being especially solicitous concerning oral hygiene; in fact, the most scrupulous general hygiene should be observed. A generous allowance of vitamin B should be included in the diet. Operative procedures on these patients should be approached with considerable caution, as the granulopenic state may develop at any time and prevent proper healing. Routine blood counts should be studied with great care, and all patients having a granulopenia should be under careful observation and frequent blood counts should be made.

*Diet.*—Diet may play a more important rôle both in etiology and in treatment than is now imagined. Doan,<sup>72</sup> experimenting with pigeons by underfeeding, reduced the red marrow of the radius to an extreme hypoplasia. There were only three component parts left: blood vessels, fat cells and a minimal residual framework of reticulum and reticular cells. Lossen<sup>73</sup> made counts of the total number of cells per cubic millimeter in children's marrow, finding that their number seemed, in a general way, to be dependent on the state of nutrition. If this can be proved and the dietary factor that has a specific influence found, it will have a most practical bearing. If, as Minot has suggested, a diet rich in vitamin B is of material aid, especially in the chronic, recurring and cyclic cases, the diet should contain a liberal supply of the following, arranged in order of vitamin content:

Excellent \* \* \* Asparagus; kidney, navy and soy beans; raw cabbage; raw tomatoes; wheat germ.

Good \* \* \* \* Heart; liver; kidney; egg yolk; milk; whole cereals; green vegetables; fresh fruit juices.

Fair \* \* \* \* Lean muscle meat.

A patient with recurring benign neutropenia, in a series of cases to be reported later, received the following daily diet during a first and

72. Doan, C. A.: *Bull. Johns Hopkins Hosp.* **33**:222, 1922; *Contrib. Embryol.* **14**:27, 1922.

73. Lossen, J.: *Virchows Arch. f. path. Anat.* **200**:258, 1920.

second attack: four egg yolks in milk (chocolate flavored), 750 cc.; tomato juice, 500 cc.; orange juice, 750 cc.; grape juice, 250 cc.; purée of pea soup, 250 cc. As soon as the patient was able to take more solid food, creamed asparagus and cooked oatmeal were added to the list. The patient gained 6 pounds (2.7 Kg.) on this diet during two weeks in bed. This diet and local treatment of the mouth and throat were the only therapeutic measures used in this case.

*Treatment of Benign and Malignant Neutropenia Due to Arsphenamine.*—Foster<sup>74</sup> successfully treated patients with "malignant" neutropenia due to arsphenamine by the intravenous use of sodium thiosulphate. Kennedy<sup>75</sup> and O'Leary and Conner<sup>76</sup> reported a similar success. The best results are to be had from the intravenous administration of sodium thiosulphate, although it can be given by mouth. McBride and Dennie<sup>77</sup> advised that it be given in not more than 20 cc. of distilled water, with daily intravenous injections for four days, and then alternate days, for as many injections as may be necessary, in doses starting with 0.3 Gm. and increasing by 0.15 Gm. daily. Sodium thiosulphate is nontoxic in doses up to 2 Gm. Dodd and Wilkinson<sup>78</sup> said that there is no specific or stimulating action attributed to transfusion in these cases. Moore and Keidel<sup>79</sup> called attention to the appearance of prodromal or warning symptoms in these patients. They are manifested by itching, mild rash, prolonged fever, malaise or any tendency toward purpura. These authors examined the blood in several cases showing such symptoms and discovered a slight decrease in the neutrophilic cells, an eosinophilia varying from 5 to 8 per cent, a slight increase in the endothelial leukocytes and the presence of numerous fragile leukocytes.

*Splenectomy.*—Splenectomy was performed in one case reported by Baldrige and Needles.<sup>8</sup> The patient died thirty-five days after the operation. There was not the usual rise of leukocytes after the operation seen in other cases, but there was the usual platelet response. At necropsy the bone marrow showed an overgrowth of myelocytes and myeloblasts almost as marked as in myelogenous leukemia. The authors commented that it was unfortunate that a biopsy specimen of the bone marrow was not obtained before splenectomy, because the part played by the splenectomy in this overgrowth of myeloid cells could have been determined.

74. Foster, J. M., Jr.: Colorado Med. **27**:388 (Oct.) 1930.

75. Kennedy, W. R.: Canad. M. A. J. **19**:439, 1928.

76. O'Leary, P. A., and Conner, H. M.: Am. J. Syph. **9**:262, 1925.

77. McBride, W. L., and Dennie, C. C.: Treatment of Arsphenamin Dermatitis, Mercurial Poisoning and Lead Intoxication, J. A. M. A. **83**:2082 (Dec. 27) 1924.

78. Dodd, K., and Wilkinson, S. J.: Severe Granulocytic Aplasia of the Bone Marrow, J. A. M. A. **90**:663 (March 3) 1928.

79. Moore, J. E., and Keidel, A.: Stomatitis and Aplastic Anemia Due to Neo-Arsphenamine, Arch. Dermat. & Syph. **4**:169 (Aug.) 1921.



*Transfusions.*—Transfusions have been used in many of the cases reported, some of the patients recovering and others dying. Transfusion is essentially empirical. No definite conclusions as to its efficacy can be drawn from my experience or from the literature. In practically all of the cases, other measures were used along with the transfusions. It is an established fact that repeated transfusions lower the rate of erythropoiesis,<sup>14</sup> and perhaps granulopoiesis. There is no evidence that transfusions actually stimulate granulopoiesis or that the neutrophils added in 500 cc. of blood would be of any assistance, as the life of the neutrophil is short (five days), and the number added would be quite small compared to the number needed. In case 2 of a series of cases reported by Conner and his associates<sup>61</sup> it is pointed out that three hours after transfusion their patient had 300 less white cells. Taking into consideration the limit of error in counting and the rhythmic delivery of granulocytes to the blood stream, it is at least evident that there was not an increase. In case 13 of a series of cases reported by Jackson and his co-workers<sup>80</sup> transfusion was followed by a reduction in white blood cells. The patient in case 16 of the same series was given a transfusion after nucleotides had caused an increase of white cells to start, and there followed a reduction in white cells. Such a reduction of white cells was not seen in the other patients treated with nucleotides alone, after a rise had started. Apparently the rate of granulopoiesis was lowered in this patient by the transfusion. The blood from a healthy donor may contain the principles to bring about normal maturation, but the amount of this substance added to the recipient also would be too small compared to the amount needed.

*Immunotransfusion.*—In June, 1930, Fisher<sup>81</sup> reported the successful treatment of a patient with "malignant" neutropenia by immunotransfusion. The patient was a nurse, aged 24, who had suffered with sore gums and malaise for two weeks. As Vincent's organisms were found on the gums, she was given 0.4 Gm. of neoarsphenamine intravenously. The next day she was much worse; sore throat developed, and she was admitted to the hospital. The white cells totaled 1,200, with 6 per cent granulocytes. The second and third days she was treated with an ordinary transfusion of 500 cc. of unmodified blood, 25,000,000 dead typhoid germs and an ampule of sodium nucleate. There was no improvement in the symptoms or the blood picture. On the fourth day of her illness, a donor of the same group, who had recovered from this disease in 1927, was secured, and 500 cc. of his blood was given to the patient. The third day after this transfusion,

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80. Jackson, H., Jr.; Parker, F., Jr.; Rinehart, J. F., and Taylor, F. H. L.: Studies of Diseases of the Lymphoid and Myeloid Tissues: VI. The Treatment of Malignant Neutropenia with Pentose Nucleotides, J. A. M. A. **97**:1436 (Nov. 14) 1931.

81. Fisher, R. L.: J. Michigan M. Soc. **29**:435 (June) 1930.

or seven days after the diagnosis had been made, the total count was 7,800, and there were 21 per cent granulocytes. (In a spontaneous recovery, improvement occurs at about this time also.) In November, 1930, Harkins<sup>69</sup> also treated a patient with "malignant" neutropenia successfully by giving a transfusion of 500 cc. of blood from a patient who had recovered from this disease. No definite conclusions can be drawn from two cases. There is not any evidence so far to indicate that any kind of immune bodies are formed in the blood stream in this disease. If a recovered patient's serum contained immune bodies, relapses and recurrences should not be the rule. One attack does not give immunity from further attacks. It does not seem advisable to put a strain on the blood-forming tissues of any patient who has had an attack of such a fatal disease. One would not use a patient who had pernicious anemia as a donor for a recipient who had the same disease.

*Transfusions and Neoarsphenamine.*—The practice of adding neoarsphenamine to the transfused blood now does not seem wise, as Farley<sup>50</sup> reviewed from the literature thirty-nine cases in which the function of the bone marrow was depressed following the use of various preparations of arsphenamine. The symptoms varied from those of purpura hemorrhagica to those of severe aplastic anemia and malignant neutropenia, depending on whether the principal effect was on the granulopoietic, megakaryopoietic or erythropoietic tissue, or on all of these combined.

*Irradiation of Bones.*—This treatment was first suggested by Friedemann.<sup>60</sup> He applied, in measured amounts, one twentieth of an erythema dose of roentgen rays to the bones of the skeleton, using a hard filter (6 mm. of copper). He irradiated the long bones in four cases, giving from one to three treatments at intervals of from two to several days. He reported that improvement from roentgen treatment may begin within from twenty-four to thirty-six hours, both in the symptoms and in the blood picture. Regarding the dosage, he said that no definite judgment can be rendered. One irradiation with one-twentieth skin unit dose may produce a blood crisis in one patient, and in another it may take three doses to produce a change in the blood picture. In 1930, Friedemann and Elkeles<sup>82</sup> published another article on roentgen treatment of this disease. The first patient given roentgen rays in this country was treated by Call and his associates,<sup>83</sup> and the technic given by Friedemann was used. Waters and Firor<sup>84</sup> reported the cases of five patients treated with roentgen rays; four are still living, and one

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82. Friedemann, U., and Elkeles, A.: *Deutsche med. Wchnschr.* **56**:947 (June 6) 1930.

83. Call, M.; Gray, B. H., and Hodges, F. M.: *Am. J. Roentgenol.* **20**:550 (Dec.) 1928.

84. Waters, C. A., and Firor, W. B.: *Bull. Johns Hopkins Hosp.* **48**:349, 1931.

was moribund when first seen. Their technic was as follows: The lower extremities, the pelvis, the upper part of the humeri and the shoulder girdles were irradiated in the course of three or four treatments. Voltage values of 200,000 with aluminum and copper filtration, both separately and combined, with effective wavelengths ranging from 0.197 to 0.161 angstrom units, were used. The measurement of dosage was effected by a dosimeter reading in roentgens, 600 units being adopted as the erythema dose, which was that agreed on at the International Conference of Radiologists at Stockholm in 1928. When such a small dose is to be used, an accurate determination is imperative. Fiessinger and his co-workers<sup>85</sup> reported that roentgen therapy may, under certain circumstances, provoke an "agranulocytic syndrome"; they reported one case. Potter<sup>86</sup> reported a case which in the first stage gave the clinical and laboratory picture of malignant neutropenia, and he stated that it terminated with the picture of myelogenous leukemia, although, judging from the laboratory reports, it was a lymphatic leukemia. It is known that lymphocytes are more easily stimulated by roentgen rays than the granulocytes. This patient was given seven irradiations of one-half erythema dose each, which is a much greater dose than that prescribed by Friedemann. Neidhardt<sup>87</sup> reported the treatment of a patient with a severe case with the roentgen rays. He used one twentieth of the erythema dose. Two hours after the treatment the cells rose from 500 to 800; eight hours later, to 1,700, and the second day, to 3,800. A second treatment was given, and eight hours later the total cells were 9,200. The granular cells steadily increased, and the clinical condition improved. Aubertin and Lévy<sup>30b</sup> said, concerning roentgen treatment: "The efficacy of radio-therapy does not appear doubtful, but it would be well to wait for further observations to appreciate its true value and to fix the rules of its application." Certainly, the attempt should be made promptly to influence this disease by the expert application of the roentgen rays, as, when expertly applied, they at least cannot harm the patient.

*Rationale of Roentgen Treatment.*—In the adult, the marrow in the shafts of the long bones is mostly adipose tissue, having little or no blood-forming function. When excessive or pathologic demand exists, there is a formation of new centers by differentiation of the myeloblasts into granular myelocytes, the adipose tissue of the bone marrow being replaced by this newly formed tissue. One theory is that irradiation may aid in the formation of this new tissue. The only way of proving just what effect, if any, the roentgen ray has directly on the yellow marrow would be through biopsy as soon as the young granulocytes

85. Fiessinger, N.; Decourt, P., and Laur, C. M.: *Sang* 5:257, 1931.

86. Potter, H. W.: *Virginia M. Monthly* 58:739 (Feb.) 1932.

87. Neidhardt, K.: *München. med. Wchnschr.* 78:711 (April 24) 1931.

were appearing in the blood stream. Some investigators say that one cannot be sure whether the apparent stimulation is the result of chemical changes in the blood or is due to the roentgen ray itself, or whether the recovery is spontaneous. Certainly, there is no evidence that a cell per se is affected by the roentgen ray other than in a destructive manner. Friedemann<sup>60</sup> said: "It is evidently essential that as large a surface of the body as possible be subjected to irradiation. Whether, thereby, a direct effect is exerted upon the bone marrow, or an indirect effect by the irradiation of other tissues is also an open question." Also, the effect of the roentgen ray may be indirect, stimulating organs of internal secretion to produce maturation products for granulocytes. Doan's<sup>19</sup> theory is that the roentgen ray benefits the type of case showing peripheral neutropenia with hyperplastic myeloid tissue. The roentgen ray in these cases brings about a primary destruction of some of the intact myeloid foci with a liberation of autogenous nucleotide, which then initiates the maturation and delivery of granulocytes from the remaining myeloid foci. From a review of the literature and following the results in the case reported by Call and his associates,<sup>83</sup> it appears that the roentgen ray might have an important rôle in the stimulation of the granulopoietic tissue, but definite proof is lacking.

*Nucleotide Therapy.*—The nucleic acids of the animal body occur mainly in combination with protein material in the so-called nucleoproteins of which they form the characteristic radicles. The amount and character of the protein with which the nucleic acid molecule is combined vary, and the acid may, in certain cases, be found in cells in a free form. Those tissues are richest in nucleic acid which contain the largest amount of nuclear material and of nucleoprotein, such as glandular tissue, thymus, spleen, liver and hematopoietic tissue. The nucleic acids are a distinct class of substances, characterized by their decomposition products. Nucleic acids on hydrolysis yield the purine and pyrimidine nucleotides. The purine nucleotides on further hydrolysis finally yield the purine bases, adenine and guanine.

The first work done on the nature of leukocytosis produced by nucleic acid was by Ames and Huntley.<sup>55b</sup> Jackson<sup>55c</sup> was the first to demonstrate that pentose nucleotide existed in normal human blood. This substance is known to exist principally in the nuclei of living cells. Doan and his co-workers,<sup>18</sup> in their experimental work with large doses of nucleic acid, showed clearly its chemotactic effect. They also found that with nucleic acid there was a leukopenia preceding the leukocytosis, owing to a temporary storage of the granulocytes in the spleen. Then they found that the granulocytes could be called from the marrow by the split products of nucleic acid, adenine and guanine, and that after giving these substances the leukocytes were not withdrawn from the circulation by the spleen, so that there was a direct leukocytosis without

the temporary leukopenia. Reznikoff<sup>88</sup> reported four cases of malignant neutropenia, in three of which the patients recovered following treatment with nucleotides. This investigator actually used purine bases, a decomposition product of nucleotides, as he himself pointed out in a later issue of the same journal.<sup>89</sup> These substances, given intravenously to rabbits, caused a marked increase in the number of neutrophilic granulocytes without any effect on the temperature or any other cells. Adenine sulphate or guanine hydrochloride obtained from the Eastman Kodak Company was used. Other therapeutic agents were used along with this, so no precise conclusions can be drawn. Jackson and his associates,<sup>80</sup> in their series of cases, used the unbroken pentose nucleotide, called nucleotide K-96, which is prepared by Smith, Kline and French Company, according to the technic of Jones and Perkins<sup>90</sup> and under the direction of the Harvard Medical School. Twenty patients were treated. Thirteen had "malignant" neutropenia, five leukopenia and neutropenia due to an infection, and two benzene poisoning. Of the thirteen patients with "malignant" neutropenia treated, seven recovered. The first sign of improvement occurred between the third and seventh day, usually on the fifth day. The total and differential counts were invariably normal in ten days, sometimes in eight. They commented: "The consistency with which the reaction occurred on or about the fifth day is of great significance. It is at this time that the reticulocyte rise begins to take place following liver therapy in pernicious anemia." This reaction would tend to show that the time for the maturation of the granulocytes is about the same as that of the erythrocytes. There is no definite experimental proof, however, that nucleotide K-96 supplies a maturation factor for granulocytes. Doan,<sup>91</sup> experimenting on normal rabbits with pentose nucleotide, produced not only an extensive degree of myeloid hyperplasia, but also an extramedullary myelopoiesis in the kidneys and spleen. This, however, is the action of pentose nucleotide on a normal marrow. This hyperplasia may be a "replacement reaction" due to the chemotactic action (normally, the calling out of cells stimulates replacement), and just what effect pentose nucleotide would have on a marrow rapidly becoming exhausted or aplastic is not known. Five of the patients with malignant neutropenia in this series<sup>80</sup> died in spite of active nucleotide therapy. This result recalls the possible difference between the pathology of benign neutropenia and of malignant neutropenia; i. e., the function of granulopoiesis was depressed, maturation had ceased, and the bone marrow was aplastic in the fatal cases, while in the benign cases of neutropenia, the function of granulopoiesis was arrested, maturation

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88. Reznikoff, P.: *J. Clin. Investigation* 9:381 (Dec.) 1930.

89. Reznikoff, P.: *J. Clin. Investigation* 9:555 (Feb.) 1931.

90. Jones, W., and Perkins, M. E.: *J. Biol. Chem.* 62:559 (Jan.) 1925.

91. Doan, A. C.: *Proc. Soc. Exper. Biol. & Med.* 29:1030, 1932.

had not ceased, and the bone marrow was not exhausted but was normal or hyperplastic, the chief fault seeming to have been in the delivery or lack of a chemotactic factor. It seems only reasonable to assume that if the cells are not developing they cannot be called to the circulation. The patients with acute cases in Jackson's series were given 0.7 Gm. of nucleotide K-96 in 100 cc. of saline solution intravenously daily for four days, and 0.7 Gm. in 10 cc. of distilled water, given in addition intramuscularly, on the same days and on each day subsequently until there was definite improvement. The intramuscular injections usually cause no reactions; the intravenous injections cause a sharp, temporary reaction at times. Jackson and his co-workers concluded: "We believe that these nucleotides may have a definitely favorable effect on the average inactive bone marrow and in certain cases of malignant neutropenia, and we believe that the substance is worth further trial in such cases."

*Calcium Gluconate.*—Hare and Childrey<sup>92</sup> reported a case of malignant neutropenia in a patient whose symptoms suggested a disturbance of the calcium metabolism. Calcium gluconate was administered, and granulocytes appeared in the blood on the fifth day following treatment. This suggested to the authors that this agent may be of therapeutic value.

#### SUMMARY.

1. The subject of benign and malignant neutropenia has been covered, and this information has been compiled in more or less textbook fashion.

2. Many names have been proposed for this disease entity, benign and malignant neutropenia seeming to be the most appropriate.

3. The two groups, benign neutropenia and malignant neutropenia, have been further subdivided into primary and secondary groups, depending on the etiology. A classification is based on this method of distinction and on the clinical course, which tends to give a mental picture of the types that make up this disease.

4. A review of the physiology of granulopoiesis is given, since the accuracy in interpreting the blood picture in primary benign and malignant neutropenia is dependent on an understanding of the underlying mechanism of granulopoiesis.

5. A review of the theories of pathogenesis of benign and malignant neutropenia is covered, and a theory is formulated based on the underlying pathology and physiology of granulopoiesis. It is suggested that in each case of neutropenia it would be advisable to determine the etiology and underlying changes in the bone marrow. Biopsies on speci-

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92. Hare, R. A., and Childrey, J. H.: Treatment of Agranulocytic Angina with Calcium Gluconate, J. A. M. A. 98:2277 (June 25) 1932.

mens of bone marrow in all cases before treatment is begun would prove or disprove the theory of an endogenous disturbance of chemotactic and maturation factors for granulocytes as being the cause of this disease.

6. The pathology of the characteristic lesions has been covered, and complete laboratory data given.

7. Symptoms, diagnosis, differential diagnosis and prognosis have been discussed.

8. A section is devoted to a theoretical consideration of the treatment for this disease, as well as a review of all forms of treatment to be found in the literature. The rationale of these treatments, when possible, has been discussed. The theory is advanced that a specific treatment for malignant neutropenia involves an investigation of the chemical maturation factors which determine the granulocytes.

#### REPORT OF CASES

I wish to report four cases: two cases of primary malignant neutropenia as described by Schultz;<sup>93</sup> one of primary subchronic recurring benign neutropenia, and one which began as a fulminating case, with recovery, and three months later recurred as a primary subchronic benign neutropenia. This classification is taken from a previous article.<sup>93</sup> The cases came under my observation at Stuart Circle Hospital in the past four years; one, case 3, was reported by Richardson;<sup>94</sup> one, case 1, was reported by Call and his associates.<sup>85</sup> Further studies have been made in case 1 since the first report.

CASE 1.—A white woman, aged 27, an American, married, eight months' pregnant and the mother of two children, was taken ill on Oct. 19, 1928, complaining of pain in the right side of the abdomen and giving all the symptoms of pyelitis. On October 20, there was a slight sore throat, which progressively became worse on the twenty-first and twenty-second. The patient entered the hospital on October 23, with the following symptoms: The larynx, nasopharynx, faucial pillars and tonsillar fossae were acutely inflamed; the gums were sore and painful, with numerous erosions; there were general malaise, slight chills and drowsiness; she had an anemic appearance; the temperature was 100.2 F.; the pulse rate, 130; there was a loss of weight of 11 pounds (5 Kg.). The spleen was not palpable, and there were no glandular enlargements. The tonsils had been removed five years previously. The present pregnancy had been normal, with only an occasional headache and some indigestion. The leukocyte and differential count made on admission showed a marked leukopenia and neutropenia, which confirmed the diagnosis (table 1). There was also marked anemia; the erythrocytes numbered 2,450,000; the hemoglobin, by the Newcomer method, was 8.45 Gm. (50 per cent). This type of anemia is frequently seen in the latter months of pregnancy. A direct smear from the throat showed streptococci; a culture showed staphylococci with streptococci predominating. Smears from the gums showed streptococci and Vincent's

93. Beck, Regena C.: *Bull. Stuart Circle Hosp.* 2:41 (Aug.) 1932.

94. Richardson, J. K.: *Virginia M. Monthly* 58:545 (Nov.) 1931.

organisms. Blood cultures made on October 23 and 29 were negative. Urinalyses made throughout the course of the disease were negative except for a trace of albumin.

On October 23, the patient was given a transfusion of 250 cc. of blood, and on October 24, 350 cc. of blood. The symptoms and blood picture had grown progressively worse during October 23 and 24, the total leukocytes on the twenty-fourth being 640. The patient was desperately ill; the cervical lymph glands were enlarged; large plugs of mucus and membrane were being discharged from the nose, and there was blood-streaked, frothy sputum. Fetal movements had ceased; the fetal heart could not be heard, and the baby was thought to be dead. On October 25, decision was made to try roentgen treatments as prescribed by Friedemann.<sup>62</sup> (This was the first patient to be treated by this method in this country.) One-twentieth of an erythema dose, using a 6 mm. aluminum filter and a distance of 50 cc., was used for two minutes over the lower extremities and over the throat. A slight improvement was noted in the blood picture on the morning of October 26, more especially in the neutrophils; by evening this improvement was quite marked, the neutrophilic granular cells having risen from 21 to 53 per cent. The total number had increased only from 700 to 875. Fetal movements returned, and the fetal heart could be heard. From October 26 to 30, improvement in the symptoms and blood picture was slow but steady, the temperature dropping to normal on October 29. On October 30, it was felt that a second roentgen treatment could be given, and it was applied over the upper extremities, and one additional minute was repeated over the femurs. On November 1, a third roentgen treatment was given. From October 30 to November 17, improvement was marked. The only treatment other than roentgen used after October 25 was supportive, with local treatment to the throat and mouth. The patient was discharged on November 17 feeling well and with a normal leukocyte and differential count; the erythrocytes numbered 3,400,000, and the hemoglobin was 9.97 Gm. (59 per cent).

On November 27, the patient entered the hospital for delivery. The next morning labor was induced. She was delivered on the afternoon of November 29 of a male child, weighing 6 pounds (2.7 Kg.) and in good condition. After delivery, the spleen was found to be 3 inches (7.6 cm.) below the costal arch, but was not sensitive, and it decreased in size in a few days. Beginning on the first day after delivery and lasting until the seventeenth day, the patient had a septic temperature, which was as high as 102 F. Blood cultures made on December 12, 15 and 28 were negative. The blood sugar was 92 mg. per hundred cubic centimeters; urinalyses gave negative results. All during this second period in the hospital the patient's lowest total count was 4,450; the lowest neutrophilic granular percentage was 26. Because of this low percentage of granular cells, another roentgen treatment was given to the long bones on December 12. The patient was discharged from the hospital on Jan. 1, 1929, with a normal blood picture and feeling well. The total erythrocytes were 3,990,000; the hemoglobin was 12.17 Gm. (72 per cent).

On January 25, the patient's total leukocytes were 4,600. On this date we tried out the hemoclastic crisis test of Widal. Two hundred cubic centimeters of milk was given on an empty stomach, and instead of the usual leukocytosis (leukocytosis developed in a normal control patient), there was a marked leukopenia (table 1). Just what the significance of this reaction is in this disease cannot be stated.

On February 12, a marked leukopenia again developed, and the patient entered the hospital for her fifth roentgen treatment, observation and study of the blood. At this time the blood culture was negative; the blood chlorides were 528 mg.;



TABLE 1.—Blood Count in Case 1\*

Date	Total White Cells	Myelo- blasts	Myelo- cytes	Juvenile Cells	Seg- mented Cells	Lympho- cytes	Endo- thelial Leuko- cytes	Other Cells	Undif- feren- tiated Cells
10/23/28	1,400	..	1	..	15	72	8	3 Türk	1
10/23/28	1,200	..	1	13	10	76			
10/24/28	1,025	..	4	4	7	81	2	1 Türk	1
10/24/28	640	..	..	14	14	60	12		
10/25/28	700	..	..	7	14	77	..	1 Türk	1
10/25/28	First roentgen treatment given								
10/25/28	733.5	..	..	..	11.5	69.5	4.5		
10/26/28	850	..	1.4	8.5	17.5	69	2.6	1 Türk	1
10/26/28	875	..	8	20	25	36	7	.....	4
10/27/28	1,050	..	1	9	36	40	2	2 Türk	1
10/27/28	750	..	6	11	26	47	6	.....	4
10/28/28	1,100	..	7	6	24	58	2	.....	3
10/29/28	1,150	..	2	10	39.5	39.5	6	2 Türk	1
10/30/28	1,713	..	4	12	34	39	2	7 Türk	2
10/30/28	Second roentgen treatment given								
10/31/28	2,825	..	1	10	39	46	2	1 Türk	2
11/ 1/28	2,980	..	1	9	49	39	1	2 Türk	2
11/ 1/28	Third roentgen treatment given								
11/ 2/28	3,225	..	1	7	53	37	2		
11/ 3/28	3,244	..	1	4.5	64.5	27.5	..	.....	0.5
11/ 5/28	5,800	..	..	4	73	22	..	1 Türk	
11/ 7/28	6,300	..	..	2.5	77	18.5	0.5	0.5 Türk	
11/ 9/28	6,750	..	..	2	79	17	2		
11/10/28	7,700	..	..	..	83	16	..	.....	1
11/12/28	8,850	..	..	..	86	13	1		
11/14/28	8,400	..	1	..	82	17			
11/16/28	7,025	..	..	..	85.5	14.5			
11/24/28	Discharged from hospital								
11/24/28	4,431	2	2	..	73	23			
11/27/28	5,600	..	1	..	73	23	..	1 Türk	2
11/30/28	Entered hospital for delivery								
11/30/28	4,750	1	1	..	64	32	1	.....	1
12/ 1/28	4,900	4	3	..	63	28	..	.....	2
12/ 3/28	4,500	..	3	1	45	46	1	.....	4
12/ 4/28	5,400	2	2	1	53	39	..	1 Türk	2
12/ 5/28	6,300	4	..	..	51	44	..	.....	1
12/ 6/28	6,700	1	..	..	52	43	1	1 Türk	2
12/ 7/28	7,300	1	..	1	63	31	..	1 Türk	1
12/ 8/28	7,300	1	..	..	49	49	1		
12/10/28	6,500	..	..	..	45	54	..	.....	1
12/11/28	5,950	1	..	..	33	62	4		
12/12/28	Fourth roentgen treatment given								
12/12/28	6,400	..	..	..	24	75.5	..	.....	1.5
12/13/28	7,750	..	..	11	15	71	2	.....	1
12/14/28	4,450	..	..	9	36	53	2		
12/14/28	4,450	..	3	18	22	62			
12/15/28	4,800	..	..	8	21	64	5	1 Türk	1
12/17/28	4,800	..	..	4	34	60	2		
12/18/28	5,400	..	..	4	24	69	3		
12/19/28	5,250	..	..	2	56	39	3		
12/20/28	4,600	..	..	4	44	50	2		
12/21/28	4,900	..	..	3	46	49	2		
12/22/28	5,600	..	..	..	44	53	3		
12/24/28	7,600	..	..	1	68	30	1		
12/26/28	7,200	..	..	2	54	42	2		
12/28/28	7,600	..	..	1	64	35			
12/31/28	6,500	..	..	1	60	38	..	1 Türk	
12/31/28	Discharged from hospital								
1/10/29	6,600	..	..	..	50	50			
1/18/29	5,650	..	..	5	31	64			
1/25/29	4,600	..	..	..	33	59	7	1 eosinophil	
1 hr. later	3,400	..	..	..	39	59	1	.....	1
2 hrs. later	4,100	Hemoclastic crisis test				30	69		
Third hr.	3,700	..	..	16	29	52	..	1 Türk	2
1/29/29	4,000	..	..	..	32	67	1		
2/ 5/29	4,200	..	..	..	27	78			
2/12/29	Entered hospital; fifth roentgen treatment given								
2/12/29	2,600	..	1	21	18	58	2		
2/13/29	2,400	..	..	8	14	78			
2/14/29	2,900	..	2	3	21	71	..	1 Türk	1
2/15/29	4,200	..	..	5	28	65	..	.....	2
2/16/29	3,400	..	..	4	18	77	..	.....	1
2/18/29	3,933	..	..	2	39	56	2	.....	1
2/19/29	3,100	..	..	7	49	42	..	.....	2
2/20/29	2,800	..	..	5	46	46	1	.....	2
2/21/29	3,400	..	..	..	49	51			

\* Where two counts appear on the same date, the first was made at 9 a. m. and the second at 4 p. m.

TABLE 1.—*Blood Count in Case 1—Continued*

Date	Total White Cells	Myelo-blasts	Myelo-cytes	Juvenile Cells	Seg-mented Cells	Lympho-cytes	Endo-thelial Leuko-cytes	Other Cells	Undif-feren-tiated Cells
2/22/29	3,200	..	..	4	47	48	1		
2/23/29	4,100	..	..	5	27	65	..	2 Türek	1
2/25/29	2,600	..	..	7	59	34			
2/26/29	3,800	..	..	..	45	54	..	1 Türek	
2/27/29	4,000	..	..	..	43	57			
2/28/29	4,450	..	..	..	48	53			
3/ 1/29	3,900	..	..	..	54	46			
	Discharged from hospital								
3/ 5/29	3,700	..	..	5	54	41			
3/ 8/29	3,500	..	..	..	38	60	..	.....	2
3/14/29	1,400	..	..	5	19	76			
3/14/29	Sixth roentgen treatment given								
3/16/29	1,500	..	..	3	29	67	..	.....	1
3/18/29	1,650	..	..	2	26	71	1		
3/21/29	2,450	..	..	2	50	48			
3/28/29	2,200	..	1	10	31	54	2	.....	2
4/ 2/29	1,450	..	..	5	29	65	..	.....	1
4/ 4/29	1,600	..	..	4	13	81	2		
4/ 5/29	1,463	..	..	11	14	72	..	.....	3
4/ 9/29	2,250	..	..	4	26	70			
4/12/29	2,537	..	..	7	39	54			
4/15/29	3,500	..	..	5	38	51	..	.....	6
3/18/29	1,850	..	..	10	38	48	..	.....	4
4/22/29	2,012	..	..	8	66	22	3	.....	1
4/27/29	2,500	..	..	..	38	62			
6/ 5/29	4,800	..	..	..	62	37	1		
6/13/29	5,800	..	..	..	70	28	2		
6/22/29	Entered hospital; diagnosis: abscess of thigh								
6/22/29	1,000	..	1	11	31	53	..	.....	4
6/24/29	2,300	..	..	11	38	47	..	.....	4
6/24/29	Discharged from hospital								
7/16/29	2,800	..	..	2	36	54	..	2 Türek	6
8/ 6/29	4,450	..	..	..	62	37			
3/20/30	8,100	..	..	..	57	42	..	1 eosinophil	
4/17/30	6,250	..	..	..	71	29			
2/ 2/31	5,075	..	..	..	64	34	1	1 eosinophil	

the carbon dioxide-combining power was 72.1. The temperature was normal, and she felt well, the only complaint being fatigue when neutropenia was present. The blood picture improved during this period in the hospital, but on March 1, when she was discharged, there were still moderate leukopenia and neutropenia.

On March 14, the total white cells were 1,400, with 24 per cent neutrophilic granular cells. On this date the patient received her sixth and last roentgen exposure, but the blood picture did not reach normal until June 13.

The patient was admitted to the hospital again on June 22 with the diagnosis of abscess of the thigh in the gluteal region. Her temperature was 100.8 F. on admission, and was normal when she was discharged on June 24. The total white cell count at this time was 1,000, with 43 per cent neutrophilic granular cells. The patient felt well except for the local discomfort.

Periods of leukopenia and neutropenia continued until March, 1930. Since this date this patient's blood picture has been normal; the erythrocytes number 4,680,000; the hemoglobin is 14.36 Gm. (85.5 per cent). She looks well, and at the time of writing is perfectly well.

*Comment.*—This case started with all the characteristics of a fulminating case, the physical signs, symptoms and blood picture becoming grave over a four day period. Roentgen treatment was given on the fifth day; improvement was noted in the blood picture on the sixth day. On the fifteenth day from the date of onset the blood picture was normal and the patient felt well. The blood picture then remained fairly normal, even during confinement, for about three months. There was then a period of primary subchronic benign neutropenia lasting

over a period of about one year. The blood picture has remained normal during the past two and one-half years, which carries the reports to the time of writing.

CASE 2.—A white woman, aged 58, an American, married and the mother of two children, was taken ill on March 22, 1929, with sore throat, backache, one slight chill and nausea; she became progressively weaker. On March 23, I was called to her home to obtain a complete blood count. The blood study confirmed the suspected diagnosis of malignant neutropenia, and she was admitted to the hospital at noon of the same day. On admission her pulse rate was 115 and the temperature, 104 F. She looked acutely ill and pale and was nauseated; the throat was inflamed, and there was ulceration on one tonsil. Immediately on admission she was given a roentgen exposure of one-twentieth erythema dose, a 6 mm. aluminum filter being used at a distance of 50 cm. A smear taken from the throat

TABLE 2.—*Blood Count in Case 2\**

Date	Total White Cells	Myelo- blasts	Myelo- cytes	Juvenile Cells	Neutro- phils	Lympho- cytes	Endo- thelial Leuko- cytes	Türk's Cells	Unclassified Cells
3/23/29	750	1	..	3	7	88	..	..	1
3/23/29	Roentgen treatment								
3/24/29 a. m.	2,000	..	..	..	6	88	..	..	6
3/24/29 p. m.	900	..	..	1	7	91	..	..	1
3/25/29	Roentgen treatment								
3/25/29	575	..	2	3	4	86	2	1	2
3/26/29 a. m.	350	..	..	..	4	90	..	2	4
3/26/29	Transfusion								
3/26/29 p. m.	600	1	..	1	4	89	2	2	1
3/28/29	413	..	2	20	2	66	..	..	10
3/29/29	1,416	1	2	10	4	66	4	6	7
3/30/29	Transfusion								
3/30/29	2,325	..	..	19	23	40	..	11	7

\* The cells that it was impossible to classify were thought to be degenerated neutrophils.

showed Vincent's organisms and staphylococci. The culture from the throat showed *Staphylococcus aureus*. The blood culture was positive, but was accidentally discarded by a technician before identification was completed. On March 25, another roentgen exposure was given. On March 26, the lesions of the mouth and throat were worse; there were dysphagia and vomiting, and the appetite was poor. The patient seemed weaker. Ten cubic centimeters of leukocytic extract and 10 cc. of whole blood were given subcutaneously in the back. On this date she was also given a transfusion, by the direct method, of 750 cc. of blood and 0.68 mg. of neoarsphenamine. Nausea, vomiting and dysphagia still continued through March 27 and 28. On March 29, she could not retain any food and was sleepy and difficult to arouse. She was given 2 cc. of boiled milk subcutaneously. The lesions of the mouth and throat had not responded to treatment. On March 30, she was given another transfusion of 700 cc. of blood. A few hours later her temperature rose to 105.6 F.; the pulse rate was 130. By evening of this day she had involuntary stools and voiding; the temperature dropped to 102.4 F.; she became cyanosed and comatose and died at 12:30 a. m. on March 31. The urine was negative at all times except for a trace of albumin. The erythrocytes numbered 4,500,000, and the hemoglobin, determined by the Newcomer method, was 12.17 Gm. (72 per cent).

*Comment.*—This was a typical case of primary fulminating malignant neutropenia in a woman, aged 58. Sore throat, backache, slight chill and nausea were the outstanding symptoms. She was sick for only two days when the first blood count showed a marked leukopenia and neutropenia, although she was said to have been in "poor health" for some years. This patient became progressively weaker and died nine days from the onset. Transfusions of blood and roentgen treatment failed to stimulate the granulopoietic tissue. On the last day there was an "agonal" discharge of the few remaining granulocytes.

CASE 3.—A white woman, aged 30, an American, married, who had no children but had had one miscarriage, was admitted to the hospital on June 19, 1930, suffering with a severe sore throat, headache, general malaise, membrane on the buccal mucous membrane, enlarged and tender anterior cervical lymph glands, a temperature of 103 F. and a pulse rate of 98. She had had a curettement for an incomplete abortion about four weeks previous to the present illness. One week following this operation sore throat with fever and slight nausea developed. (This may have been a first attack of neutropenia.) The symptoms abated in a few days, and she felt well again. On June 17, she was again taken ill, suffering with sore throat, headache and general malaise. The temperature at this time was 101 F., the pulse rate, 95, and there were marked stomatitis and pharyngitis. On June 18, the symptoms were more marked, with a slight enlargement of the anterior cervical lymph glands. A blood count at this time revealed a marked leukopenia and a total absence of granular cells. She entered the hospital on June 19 with a diagnosis of malignant neutropenia. Smears from the throat showed staphylococci, rare Vincent's organisms, fusiform bacilli and rare streptococci. Culture from the throat showed streptococci and staphylococci, *Bacillus pyocyaneus* predominating. The erythrocytes numbered 4,201,000, and the hemoglobin, determined by the Newcomer method, was 12 Gm. (71 per cent). The urine contained a slight trace of albumin and a few pus cells. (These pus cells may be explained by a few of the remaining neutrophils being eliminated onto the mucous membranes, a normal method for their destruction.)

The patient was given three roentgen exposures to the long bones, according to the method of Friedemann, on June 19, 20 and 21, but there was little evidence that it had stimulated the granulopoietic tissue. On June 20, it was felt that there had been a slight benefit due to the increase of granular cells from 10 per cent on the afternoon of June 19 to 28 per cent on the morning of June 20. However, the total count was lower, so that it was interpreted as a degenerative shift. Ten cubic centimeters of leukocytic extract and 5 cc. of sterile milk were administered on June 21, and 10 cc. of leukocytic extract on June 22 and 23. The physical signs and symptoms progressively grew worse, and the patient died on the morning of June 23.

Permission was given to examine the abdominal cavity and obtain a section of bone. The negative findings will be omitted. In the ilium five small ulcers were found having a crater diameter of 2 mm., with a hemorrhagic area surrounding them. Acute inflammatory reaction was absent. The appendix had been removed at a previous operation. The omentum was adherent to the ilium at various points on its anterior surface and was also adherent to the pelvic organs. The adhesions were old and fibrous. There was slight congestion of the mesenteric blood vessels. The liver was slightly enlarged and congested and microscopically showed only parenchymatous hypertrophy. The spleen was slightly darker than normal, with

moderate congestion; microscopically, there was moderate fine fibrosis. The kidneys showed moderate congestion; microscopically, there was a moderate amount of parenchymatous hypertrophy, with a moderate amount of hemorrhage into the interstitial substance. The uterus was normal in appearance, with atrophic endometrium, and was negative for necrosis or membrane formation. The fallopian tubes showed a marked congestion and marked chronic salpingitis. The right ovary was enlarged, 5 by 5 by 4 cm., and contained hemorrhagic and simple cysts. The left ovary had been removed at a previous operation. Grossly, the bone marrow of the tibia, rib and sternum was bright red and seemed to consist of red trabeculae and pale fluid fat. Microscopically, the hematopoietic tissue showed normoblasts, giantoblasts and megakaryocytes. An occasional cell resembling a myeloblast was found, but they showed so much degeneration it was impossible to classify them definitely. A culture taken from the bone marrow showed a pure growth of *Bacillus pyocyaneus*.

TABLE 3.—*Blood Count in Case 3\**

Date	Total White Cells	Myelocytes	Juvenile Cells	Neutrophils	Lymphocytes	Endothelial Leukocytes	Unclassified Cells
6/19/30 a. m.	650	..	3	..	95	2	..
p. m.	Roentgen treatment 888	2	8	..	84	2	..
6/20/30 a. m.	633	11	9	8	83	..	2
p. m.	Roentgen treatment 859	7	6	1	80	..	2
6/21/30 a. m.	500	..	1	..	86	2	8
p. m.	Roentgen treatment 553	..	6	..	84	..	4
6/22/30 a. m.	475	..	6	..	80	10	4
p. m.	Roentgen treatment 775	4	8	..	84	..	4
6/23/30 a. m.	3,180	..	2	..	92	2	4

\* The unclassified cells were thought to be degenerated neutrophils.

*Comment.*—This is a typical case of primary fulminating malignant neutropenia in a patient who probably had had an attack of neutropenia one week following curettage. Just what bearing the curettage had on this case cannot be said, but during the illness there were no symptoms referable to the pelvic organs, and at autopsy there was no erosion or membrane formation in the vagina or the uterus. The agonal leukocytosis was due to an increase of lymphocytes, there being 2,925.6 lymphocytes in the last count.

CASE 4.—A white woman, aged 37, an American, married and the mother of one child, was taken ill on Feb. 7, 1931, with mild sore throat and acute gingivitis; her temperature rose to 101.1 F. For three months previous to this date she had complained of weakness on exertion, general lassitude, occasional sore throat and gums, slight neuritic pains in the right shoulder, headaches and a loss of 10 pounds (4.5 Kg.). As it was thought that these symptoms were possibly due to a mild secondary anemia (erythrocytes, 3,200,000; hemoglobin, 11.5 Gm. [68 per cent]), the patient had been taking liver extract (Valentine's), a compound of ferrous carbonate and ultraviolet ray treatments for the three months preceding the illness. The anemia improved—the hemoglobin was 14.02 Gm. (83 per cent) and the

erythrocytes numbered 4,070,000—but the symptoms continued. From February 1 to 7, the weakness was extreme. On February 6 the patient was unable to eat, and sleep was impossible, owing to the painful gums. On February 7, the patient was unable to leave her bed. The gums were extremely swollen and painful, and the submaxillary glands were swollen and tender. Other physical signs were negative except for a slight bronchitis and a moderately enlarged spleen. The pulse rate was 130, tumultus and irregular. The patient was drowsy and listless and complained of headache. The leukocyte and differential count disclosed a marked leukopenia and moderate neutropenia. Smears from the gums and throat showed streptococci. Cultures from the gums and throat gave a pure growth of streptococci. A dentist was called in consultation to treat the gums, and necrosis was found posteriorly in the region of the upper left incisor. The only other treatment given this patient was rest and a large amount of liquid diet rich in vitamin B, as follows: four egg yolks in milk (chocolate flavored), 750 cc.; tomato juice, 500 cc.; orange juice, 750 cc.; grape juice, 250 cc., and purée of pea soup, 250 cc. This amount was given daily, divided into five meals and administered every three hours. As soon as the patient was able to take more solid food, creamed asparagus and cooked oatmeal were added. (The patient gained 6 pounds [2.7 Kg.] on this diet during the two weeks in bed.)

The swelling of the gums was subsiding in twenty-four hours; the temperature was normal in three days, and there was gradual but steady improvement in the symptoms and the blood picture. At the end of seven days the gums were fairly well healed, and the blood picture was practically normal. Severe night sweats, involving the head, neck and chest, began at the end of the first week and continued until the end of the fourth week. Weakness persisted for four weeks, and the cardiac symptoms subsided as the weakness decreased. Other laboratory reports were as follows: The basal metabolism was minus 17; urinalyses showed a faint trace of albumin, rare hyaline casts and from 1 to 4 plus bacteria; concentration and dilution tests were normal; a phenolsulphonphthalein test gave a return of 50 per cent in two hours; the blood urea was 34 mg. per hundred cubic centimeters; the blood uric acid was 4.5 mg. per hundred cubic centimeters; the blood sugar was 105 mg. per hundred cubic centimeters; a serum bilirubin test showed less than 2 mg.; the Wassermann reaction was negative. The leukocyte and differential count did not maintain a normal level until March 24. The hemoglobin and erythrocytes always remained normal.

On August 6, there again was a leukopenia of 2,400, but the granular cells were 60 per cent. The only symptoms at this time were weakness and lassitude. (It might be noted here that although the percentage of granular cells was 60, there were only 1,440 total granular cells per cubic millimeter, whereas with a normal count there are about 4,080 per cubic millimeter. This demonstrated the necessity of taking the total granulocyte count into consideration in these cases.) On October 8, all of the signs and symptoms of appendicitis developed, with a fever and a leukocytosis of 11,900. Operation was refused. On October 12, the temperature, leukocytosis and symptoms had subsided. The blood picture then remained normal until December 18. The blood counts were then discontinued at the patient's request.

On Jan. 13, 1932, the symptoms of neutropenia again appeared, which the patient was then able to recognize. The neutropenia was more marked than during the first attack. The hemoglobin and erythrocytes were normal. On January 15, the patient was forced to go to bed because of lassitude, weakness and drowsiness, and she slept nearly forty-eight hours. There were no lesions of the mouth during this second attack, probably due to the rigid oral hygiene practiced in the interim.

TABLE 4.—*Blood Count in Case 4\**

Date	Total White Cells	Eosino- phils	Myelo- cytes	Juvenile Cells	Seg- mented Cells	Lympho- cytes	Endo- thelial Leuko- cytes	Other Cells	Undif- feren- tiated Cells
2/ 7/31	1,575	..	2	8	18	66	3	.....	3
2/ 7/31	1,266	..	8	11	27	49	1	.....	4
2/ 8/31	1,900	..	3	9	56	29	1	.....	2
2/ 9/31	2,250	..	4	3	35	52	5	.....	1
2/10/31	2,268	..	3	4	49	41	..	1 Türk	2
2/11/31	4,833	..	2	3	47	46	1	1 Türk	
2/13/31	3,375	..	..	2	65	30	2	1 Türk	
2/15/31	5,530	..	..	..	62	31	5	.....	2
2/18/31	4,650	1	..	..	69	26	3	.....	1
2/20/31	5,320	..	..	..	82	16	1	.....	1
2/23/31	4,050	..	1	..	70	25	3	.....	1
2/25/31	4,981	..	2	..	73	20	5	.....	
2/27/31	5,690	..	..	..	71	23	4	.....	2
3/ 3/31	4,957	..	1	..	54	42	1	.....	2
3/ 4/31	5,140	..	..	..	71	25	3	.....	1
3/ 6/31	4,860	..	2	..	57	35	5	.....	1
3/10/31	6,000	..	..	4	64	27	5	.....	
3/13/31	5,450	..	1	..	53	40	5	.....	1
3/17/31	3,410	..	2	..	60	31	5	1 Türk	1
3/18/31	4,430	..	..	..	61	31	6	.....	2
3/20/31	5,030	..	1	..	60	35	4	.....	
3/24/31	5,800	..	2	..	64	28	5	.....	1
3/27/31	5,640	..	2	..	65	28	4	1 Türk	
3/31/31	6,475	..	1	..	70	24	5	.....	
4/ 3/31	5,850	..	..	..	77	22	1	.....	
4/ 8/31	5,900	..	..	1	65	33	1	.....	
4/15/31	6,000	..	..	..	72	25	3	.....	
4/23/31	6,150	2	2	..	60	34	2	.....	
4/29/31	5,850	1	2	..	70	22	5	.....	
5/11/31	6,100	..	..	..	67	31	2	.....	
6/ 3/31	8,840	..	1	..	80	17	2	.....	
6/16/31	4,522	..	1	..	66	33		.....	
7/ 1/31	4,200	1	..	..	72	24	3	.....	
7/17/31	5,450	..	..	..	83	16	1	.....	
8/ 6/31	2,400	..	9	..	51	35	1	.....	4
8/ 7/31	3,530	..	9	..	61	30		.....	
8/ 8/31	3,875	..	7	..	57	33	2	.....	1
8/10/31	3,850	..	2	..	67	31		.....	
8/11/31	5,300	..	2	..	64	33	1	.....	
8/13/31	5,740	..	1	..	62	35	2	.....	
8/29/31	4,400	..	..	..	62	32	3	.....	3
10/ 9/31	9,325	2	1	..	70	27		.....	
10/10/31	11,900	1	3	..	86	10		.....	
10/12/31	6,800	1	..	..	71	27	1	.....	
12/ 3/31	7,800	1	..	1	60	33	5	1 basophil	
1/13/32	1,945	..	..	..	14	78	7	1 basophil	
1/14/32	2,100	..	..	..	21	74	2	1 Türk	2
1/15/32	2,030	..	..	2	10	83	4	.....	1
1/16/32	1,600	2	..	3	18	71	5	1 basophil	
1/18/32	3,200	..	..	2	45	50	2	.....	1
1/19/32	3,900	..	..	..	58	40	1	.....	1
1/20/32	5,300	1	..	..	69	27	..	.....	1
1/21/32	5,250	..	..	..	72	28		.....	
1/22/32	6,950	1	..	..	68	26	5	.....	
1/25/32	5,625	2	..	..	64	31	2	1 basophil	
1/28/32	6,900	..	..	..	77	21	..	1 basophil	
2/ 1/32	6,300	1	..	..	60	37	1	.....	1
2/ 5/32	8,800	..	..	..	74	25	1	.....	1
2/ 8/32	6,600	1	..	..	64	33	1	.....	1
2/11/32	3,900	3	..	..	38	54	4	.....	
2/12/32	4,566	1	..	..	58	41		.....	1
2/15/32	4,950	3	1	..	56	37	2	.....	1
2/18/32	5,622	2	..	..	64	31	2	.....	
2/24/32	6,400	2	..	..	63	34	1	.....	
2/29/32	10,750	..	..	..	64	28	6	2 Türk	
3/ 1/32	8,925	2	..	..	71	22	3	1 basophil	
3/ 4/32	7,283	..	..	1	70	23	6	.....	
3/10/32	6,500	2	..	..	63	33	1	.....	1
3/12/32	4,450	3	..	..	75	16	4	.....	2
3/14/32	4,200	1	..	..	64	33	1	.....	1
3/19/32	6,614	1	..	..	57	40	1	.....	1
3/29/32	8,220	2	..	..	78	19	1	.....	
4/ 5/32	7,510	3	..	..	62	32	2	1 basophil	

\* For purposes of brevity, the stab or rod nuclears have been included with the segmented forms. They were absent during the leukopenia, and there was never more than 7 per cent at any other time.

The cardiac symptoms were the same as in the first attack. The same treatment of rest and diet was instituted. In six days from the onset, the leukocytes rose to 5,300, with a normal neutrophilic granular percentage. At the end of a week, the night sweats again appeared, continuing for two weeks. Weakness lasted four weeks; the cardiac symptoms disappeared in four weeks. This patient had felt unusually well since the latter part of February, and was well at the time of writing.<sup>95</sup>

*Comment.*—This is apparently a typical primary subchronic recurring benign neutropenia. The patient did not give a history of any previous infection except gingivitis in 1925. A blood count was not made, so that neutropenia may have been present at that time. The patient stated that she had similar attacks in the early spring of 1929 and 1930, but thought it was influenza, and the blood was not examined. This patient did not enter the hospital, but was treated as an outpatient; she is still under observation.

#### SUMMARY OF CASES

These patients did not give a history of exposure to any of the physical or chemical agents known to produce benign or malignant neutropenia, nor did they give a history of any previous infection which might have had a bearing on the disease.

The clinical picture at the inception of the illness was the same for all four cases, case 4 having a more gradual onset.

These cases suggest that there is a fundamental difference in the pathologic changes underlying the recovered and the fatal cases. In the fatal cases, the maturation of granulocytes had ceased and the granulopoietic tissues were exhausted. A maturation factor for granulocytes has not yet been discovered so that a specific treatment could not be applied. In the recovered cases, maturation was arrested and the granulopoietic tissues were not exhausted, the fault seeming to be in the lack of a chemotactic factor to call the granulocytes to the circulating blood. In case 1, the roentgen ray in some unknown way stimulated this function to normal. Doan's<sup>19</sup> theory is that the roentgen ray brings about a destruction of some of the intact myeloid foci with a liberation of autogenous nucleotides, which then initiate the maturation and delivery of granulocytes from the remaining myeloid foci. In case 4, which was more mild, this function righted itself in time to prevent irreparable damage.

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95. This case has been studied for another year (April 5, 1932, to May 1, 1933). The history was the same with a third attack of neutropenia in March, 1933. This case appears to present an annual cycle.



# CHOLESTEROL AND LECITHIN PHOSPHORUS IN THE PLASMA OF ANEMIA OTHER THAN PERNICIOUS ANEMIA

INFLUENCE OF THERAPEUTIC MEASURES ON THESE  
CONSTITUENTS

GULLI LINDH MULLER, M.D.

AND

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BOSTON

A disturbance of cholesterol and lecithin metabolism frequently accompanies anemia. The literature<sup>1</sup> reveals, however, a considerable variation in the results obtained by many observers, even when allowance is made for differences in technic. This variation may be partly due to deficient observations on the same patient and failure to correlate the various factors involved. In pernicious anemia there is a definite relationship between the stage of the disease and the lipoids of the blood.<sup>2</sup> Cholesterol and, in many instances, the plasma lecithin phosphorus are decreased during a relapse, but as remission is inaugurated there occurs a sudden rise in the lipoids of the blood, concomitant with the reticulocyte response. This reaction develops before there is significant alteration in the concentration of the red blood cells or hemoglobin, and is apparently proportional to the rate of remission.

In so-called secondary anemia, which is usually of the hypochromic type, the literature reveals only fragmentary and conflicting data.<sup>1</sup> Some investigators state that there does not seem to be any characteristic difference in the blood lipoids in different types of anemia.<sup>3</sup> This led certain observers to conclude that the degree of anemia is directly

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1. Muller, G. L.: The Cholesterol Metabolism in Health and in Anemia, *Medicine* **9**:119, 1930.

2. Muller, G. L.: The Relation of Cholesterol, Lecithin Phosphorus and Fatty Acids to the Remission of Pernicious Anemia, *Am. J. M. Sc.* **179**:316, 1930.

3. (a) Bloor, W. R., and MacPherson, D. J.: The Blood Lipoids in Anemia, *J. Biol. Chem.* **31**:79, 1917. (b) MacAdam, W., and Shiskin, C.: The Cholesterol Content of the Blood in Anaemia, and Its Relation to Splenic Function, *Quart. J. Med.* **16**:193, 1923.

related to the level of blood cholesterol.<sup>4</sup> Köhn<sup>5</sup> concluded that low values are found in all hypochromic anemias. Bloor<sup>3a</sup> considered the disturbance of the lipid metabolism in anemias as a general reaction to the loss of cells and hemoglobin from the circulating blood, and he believed that low values of lecithin may be regarded as due to deficient assimilation of fat from the lack of sufficient corpuscles to bring about the change.<sup>6</sup>

It is obvious that knowledge concerning the blood cholesterol and lecithin phosphorus in so-called secondary anemias is fragmentary. Few data have been correlated with the stage and precise type of anemia, or with the state of the hematopoietic organs and alterations induced by therapy. We have studied sixty-one cases of various types of anemia other than pernicious anemia from these points of view (table 1).

TABLE 1.—*Classification of Cases*

	Number of Cases
Anemia due to chronic loss of blood.....	10
Anemia due to acute loss of blood.....	10
Idiopathic hypochromic anemia with and without the association of faulty diet	15
Carcinoma .....	6
Myelogenous leukemia .....	6
Idiopathic aplastic anemia.....	3
Splenic anemia .....	3
Pulmonary tuberculosis .....	1
Nontropical sprue .....	1
Osteomalacia .....	1
Osteosclerotic anemia .....	1
Hodgkin's disease .....	1
Tuberculous adenitis .....	1
Myxedema .....	1
Myeloma and plasma cell leukemia.....	1
Total.....	61

## PROCEDURE AND METHODS

Determinations of plasma cholesterol and lecithin phosphorus were made by methods employed previously.<sup>7</sup> In thirteen of the sixty-one cases only one determination was made, but the remainder were studied repeatedly for weeks or months.

4. (a) Schnabel, T. G.: Blood Cholesterol in Gastro-Enterologic Cases, *Am. J. M. Sc.* **160**:423, 1920. (b) Strathmann-Herweg, H.: Untersuchungen über den Cholesteringehalt des Blutserums, *Monatschr. f. Kinderh.* **19**:20, 1920. (c) Dönömac, I.: Ueber das Blutlipoid bei Ankylostomiasisanämien, nebst einem Anhang über den Blutzucker, das Serumeiweiss und die Senkungsgeschwindigkeit der roten Blutzellen, *Jap. J. M. Sc. Tr.* **1**:385, 1927.

5. Köhn, H.: Ueber den Cholesterinspiegel im Serum bei der perniziösen Anämie, *Deutsches Arch. f. klin. Med.* **148**:357, 1925.

6. Bloor, W. R.: The Distribution of the Lipoids ("Fat") in Human Blood, *J. Biol. Chem.* **25**:577, 1916.

7. Muller, G. L., and Talbott, J. H.: The Effect of High Altitudes on the Cholesterol, Lecithin and Fatty Acids in the Plasma of Healthy Men, *Arch. Int. Med.* **47**:855 (June) 1931.

# RELATION OF CHOLESTEROL AND LECITHIN PHOSPHORUS TO RED BLOOD CELL AND HEMOGLOBIN CONCENTRATION

Before discussing the types of anemia, we shall consider the relation of anemia per se to the plasma cholesterol and lecithin phosphorus.

In chart 1 *A*, three hundred and fifteen determinations of cholesterol have been plotted against the numbers of the red blood cells per cubic

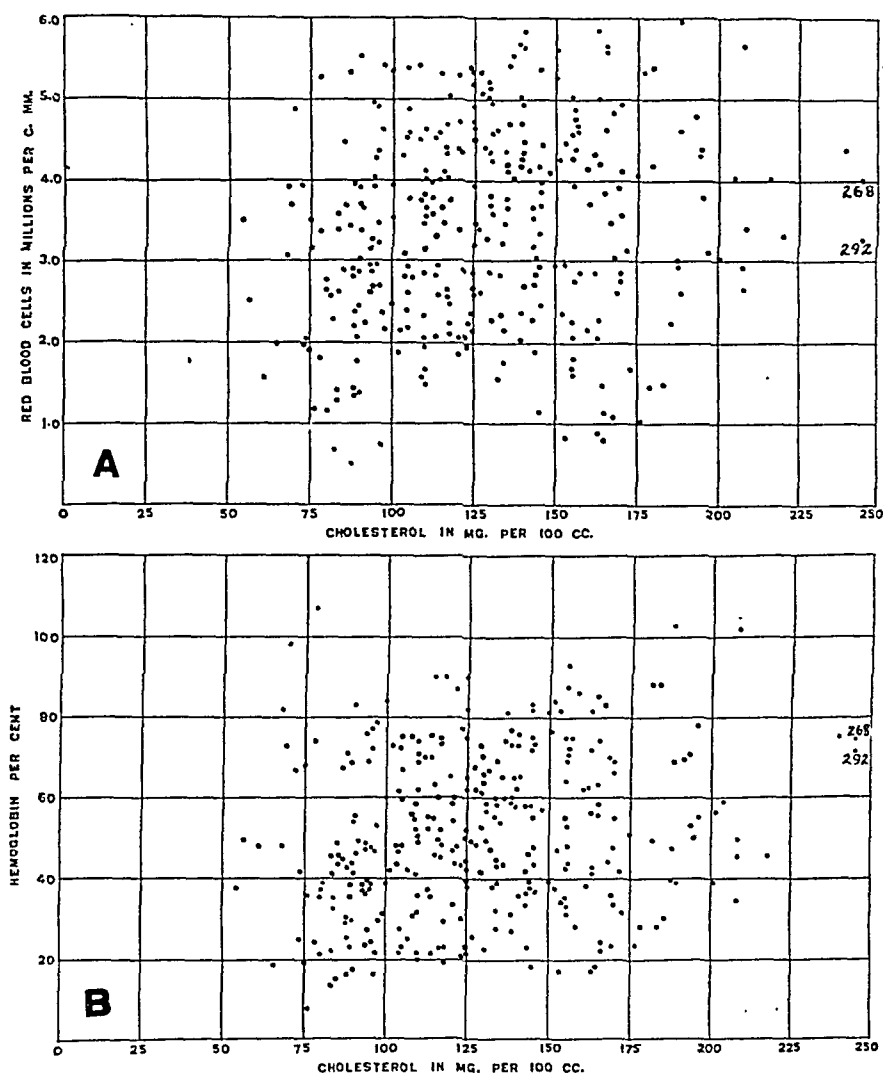


Chart 1.—Cholesterol in secondary anemia. The amount of cholesterol in the blood plasma of sixty-one patients with anemia other than pernicious anemia plotted against (*A*) the number of red blood cells and (*B*) the concentration of hemoglobin.

millimeter in the peripheral blood. The values of cholesterol range from 54 to 292 mg. per hundred cubic centimeters of plasma, and the red blood cells vary from 500,000 to 5,900,000 per cubic millimeter; but low values of cholesterol were found when the red blood cells were over 5,000,000, as well as when they were below 1,000,000 per cubic millimeter. Conversely, high normal values of cholesterol were frequently found when the red blood cells were few.

In chart 1 *B* the level of plasma cholesterol is plotted against the percentage of hemoglobin. These charts, as well as the data for pernicious anemia,<sup>2</sup> indicate that no general statement can be made as to the relation between the concentration of red blood cells or hemoglobin and the concentration of plasma cholesterol in anemia. The same con-

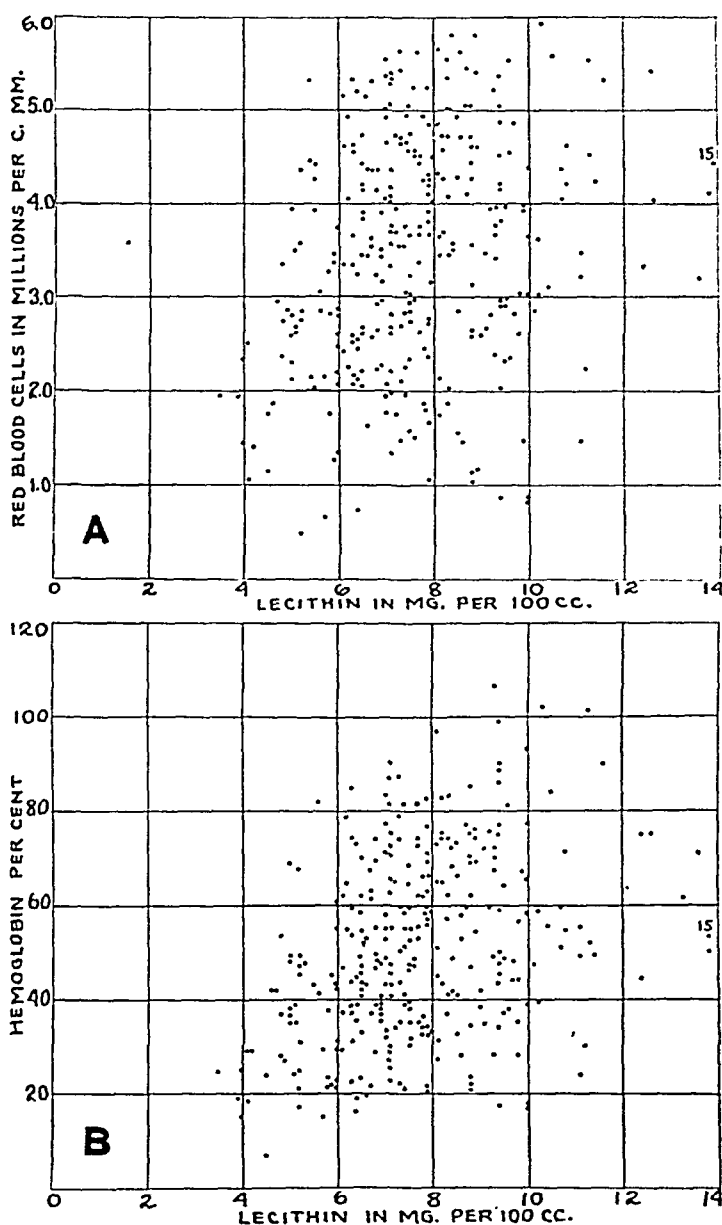


Chart 2.—The relation of the plasma content of lecithin phosphorus at various stages of anemia other than pernicious anemia to (*A*) the number of red blood cells and (*B*) the concentration of hemoglobin.

clusion can be drawn with regard to the lecithin phosphorus (chart 2). Whatever may be the underlying cause of disturbed lipid metabolism, anemia per se is not directly related to the level of the cholesterol and lecithin phosphorus in the blood.

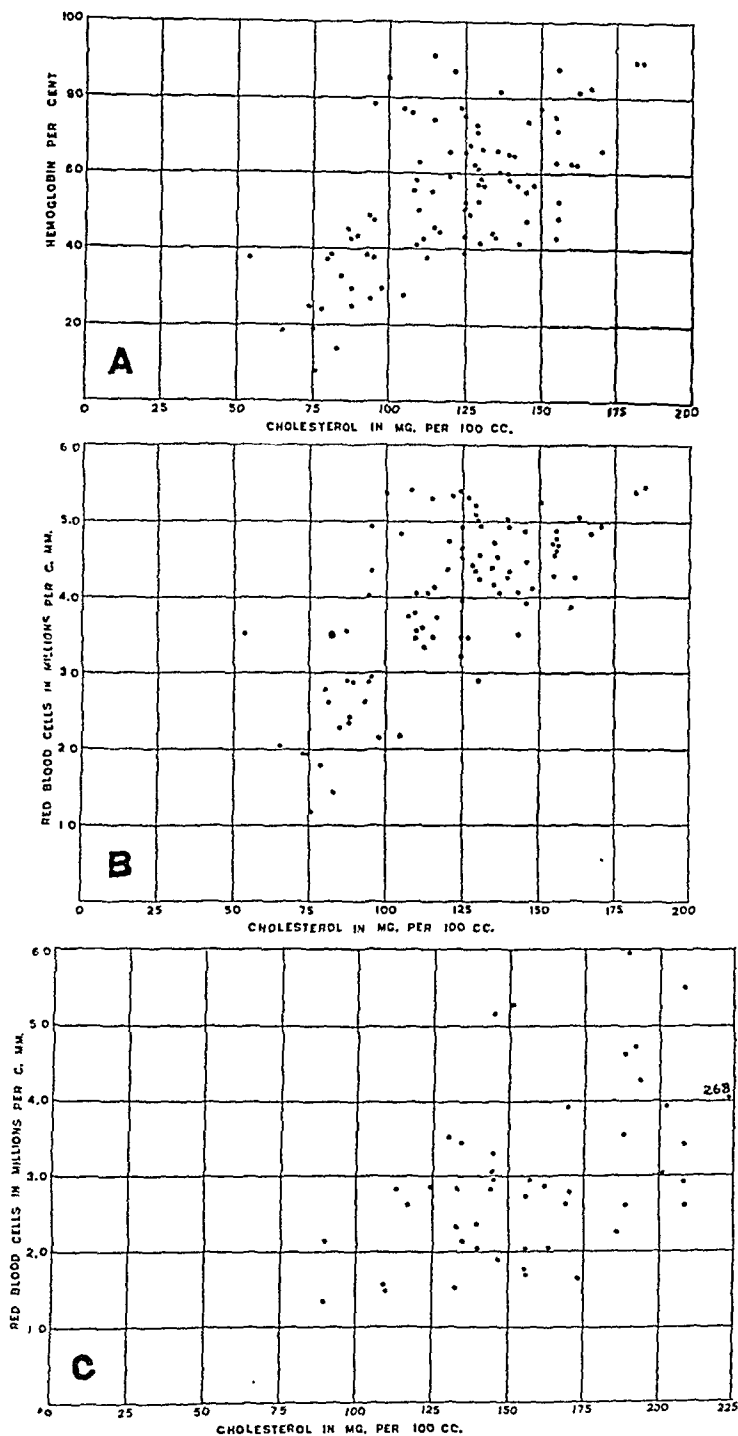


Chart 3.—Cholesterol in anemia due to hemorrhage. The relation of plasma cholesterol (*A*) to the hemoglobin, and (*B*) to the red blood cells in ten cases of anemia caused by chronic loss of blood, and (*C*) to the red blood cells in ten cases of anemia caused wholly or in part by acute hemorrhage. Note the normal or high values in comparatively severe cases of anemia due to acute loss of blood. The lowest values recorded occurred in three cases in which chronic slight loss of blood had occurred.

Although there is no correlation between the degree of anemia and the levels of the lipoids, these levels sometimes in certain types of anemia besides pernicious anemia manifest certain definite characteristics.

#### LIPOIDS IN ANEMIA DUE TO CHRONIC LOSS OF BLOOD

The relationships of cholesterol to hemoglobin and to red blood cells in the ten cases of anemia due to chronic loss of blood are illustrated in chart 3. The data for lecithin phosphorus plotted in the same manner show exactly the same relationships (chart 5 *A*). It is evident that in anemia due to chronic loss of blood both cholesterol and lecithin phosphorus tend to be low when the anemia is severe, which is more evident when the concentration of hemoglobin, rather than the level

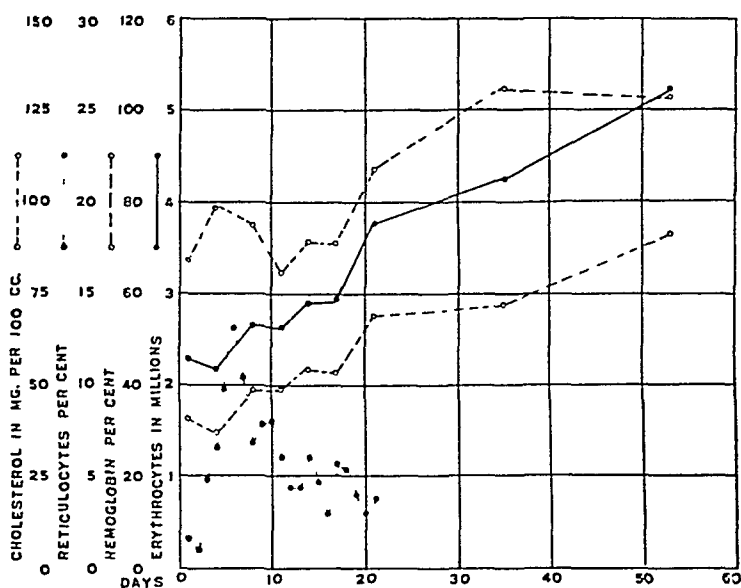


Chart 4.—Cholesterol, red blood cells, hemoglobin and reticulocytes in a patient with anemia due to a chronic loss of blood. Iron and ammonium citrate were given in large doses. The cholesterol began to increase when the reticulocyte response subsided, or about three weeks after iron therapy was begun.

of red blood cells, is considered. With improvement which in the absence of complications was readily brought about by adequate doses of iron, both the lecithin phosphorus and the cholesterol rose gradually to within normal limits.

In four of these cases there occurred a marked reticulocyte response to iron therapy. In the other six, in which there was less anemia, the reticulocyte reaction was relatively slight. The relation of the reticulocyte response to the cholesterol level in one case is illustrated in chart 4. On comparing the reticulocyte reaction in these patients with that in patients with pernicious anemia treated with liver or other potent material,<sup>2</sup> there is discernible a marked and possibly significant difference. In pernicious anemia the rise of cholesterol, and in many instances,

of lecithin phosphorus, is concomitant with the increase of reticulocytes, while in anemia associated with chronic loss of blood, the cholesterol remains low during the increase of reticulocytes, but as the reticulocytes decrease the lipoids become augmented. In anemia of this type, as is illustrated in chart 4, the rise of the concentration of red blood cells and hemoglobin is considerable before cholesterol and lecithin phosphorus are increased.

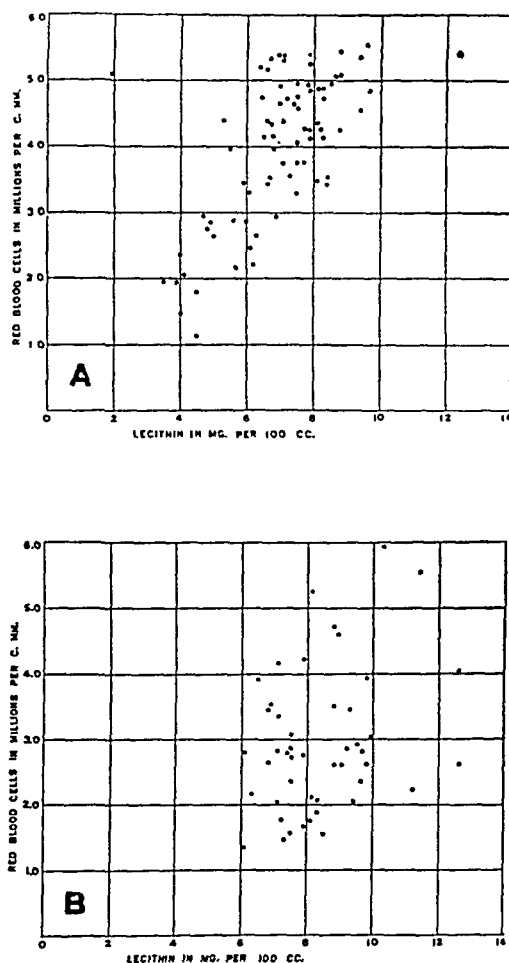


Chart 5.—Lecithin phosphorus in anemia due to hemorrhage, plotted against the red blood cells in (A) ten cases caused by chronic loss of blood and (B) ten cases caused wholly or in part by acute hemorrhage.

Intercurrent infection developed in two of the ten cases and caused fever. This was accompanied by a moderate fall of cholesterol and lecithin phosphorus from the previous level.

#### LIPOIDS IN ANEMIA DUE TO ACUTE LOSS OF BLOOD

No previous loss of blood had occurred in five of the ten patients with anemia especially due to acute loss of blood. In at least three there had been recurrent slight loss of blood from the gastro-intestinal

tract before the sudden loss of blood that particularly induced anemia. Thus, the reserve supplies of blood-building material in the latter patients were diminished, so that they may be considered intermediate in type between those with no previous loss of blood and the ten with chronic loss of blood of considerable degree. In most instances the observations were not made immediately after the hemorrhage.

The relation of cholesterol and lecithin phosphorus to the red blood cells is illustrated in charts 3 *C* and 5 *B*, respectively. Similar charts were obtained from plotting data for the lipoids against the percentage of hemoglobin, as the color index was usually close to unity. Contrasting *C* with *A* and *B* in chart 3 and *A* with *B* in chart 5, it is evident that the behavior of the lipoids differs in anemia due to chronic loss of blood and that due to acute loss of blood. In the five uncomplicated cases of anemia due solely to acute hemorrhage, the lipoids were within the normal range, but the degree of anemia was as great as in the cases due to chronic loss of blood, in which the cholesterol and the lecithin phosphorus were below normal.

The few subnormal values of cholesterol obtained in the cases in which acute loss of blood was particularly responsible for the anemia (chart 3 *C*) occurred in three cases in which there had been bleeding previously. Transient infection accounted for decreased plasma lipoids in two observations.

Reticulocyte responses to the acute loss of blood occurred in all ten cases. The relation of the plasma lipoids to the reticulocyte response in the cases differed from that seen in cases caused by chronic loss of blood. As a rule, the outpouring of reticulocytes following the acute hemorrhage was accompanied by hypercholesterolemia and lecithinemia. In three patients in whom the acute hemorrhage was superimposed on chronic loss of blood the plasma lipoids were decreased and the lowest values were concomitant with the peak of the reticulocyte response. The results in these three cases simulated those in cases of anemia due to chronic loss of blood, which is not surprising because the patients had had a slight chronic loss of blood formerly. This recurrent slight drain on the formation of blood thus appears to have affected the cholesterol in the direction that it takes after repeated and pronounced chronic loss of blood.

#### LIPOIDS IN IDIOPATHIC HYPOCHROMIC ANEMIA WITH AND WITHOUT ASSOCIATION OF FAULTY DIET

Of the fifteen patients with this chronic condition, nine had achlorhydria and the rest hypochlorhydria. Determinations were made of the lipoids, red blood cells and hemoglobin at least weekly, and the reticulocytes were counted daily during the early days of iron therapy. Eleven



cases were studied for periods varying from five to eighteen weeks, while the four remaining cases were observed for shorter intervals.

The surprising fact is that in this group there is no positive and consistent relationship between the cholesterol or the lecithin phosphorus and the concentration of hemoglobin or red blood cells, color index or reticulocyte response to iron. Data for six cases of hypochromic anemia with achlorhydria are given in table 2. It is evident that neither in pernicious anemia (hyperchromic) nor in idiopathic hypochromic anemia are the levels of blood lipoids related to achlorhydria.

In seven of fifteen patients with varying degrees of anemia the plasma cholesterol and lecithin phosphorus were within a narrow normal range throughout. In the remaining cases, except two, the lipoids varied considerably at a level that was subnormal or near the lower

TABLE 2.—*Red Blood Cells, Hemoglobin, Cholesterol and Lecithin Phosphorus in Idiopathic Hypochromic Anemia with Achlorhydria*

Patient	Sex	Age	Time of Observations in Weeks	Red Blood Cells, Millions per C.Mm.		Hemoglobin, per Cent		Cholesterol, Mg. per 100 Cc. of Plasma		Lecithin Phosphorus, Mg. per 100 Cc. of Plasma	
				Low	High	Low	High	Low	High	Low	High
1	♀	47	13	3.4	5.3	41	85	94	131	6.2	8.0
2	♀	44	18	4.2	5.5	47	83	87	125	5.3	8.2
3	♀	32	15	3.9	5.4	39	74	85	150	5.0	8.9
4	♀	33	9	4.4	5.5	62	74	140	166	8.3	8.8
5	♀	42	10	2.1	4.6	28	85	156	165	7.9	9.4
6	♀	25	12	5.0	5.8	55	83	139	155	7.0	8.4

limit of normal. The values recorded, however, showed no definite trend, but were frequently highest at a time when the anemia was most severe.

In two patients the anemia was severe, with 1,300,000, and 2,200,000 red blood cells per cubic millimeter and 16 and 22 per cent hemoglobin, respectively. In both cases the cholesterol and lecithin phosphorus were somewhat low at the height of the anemia. In each case there was a rise of both cholesterol and lecithin phosphorus before the reticulocyte response to iron had subsided, comparable to what occurs in pernicious anemia (chart 6).

#### LIPOIDS IN ANEMIA ASSOCIATED WITH CARCINOMA OF THE STOMACH

In five of the six cases of carcinoma of the stomach the hypochromic anemia could be attributed, at least in part, to chronic loss of blood, and in only one was there a significant decrease of anemia. In all of the cases the cholesterol values were below 125 mg. per hundred cubic centimeters (chart 7), and the lecithin phosphorus was below 7 mg. per hundred cubic centimeters regardless of the level of red blood cells, hemoglobin and reticulocytes, except in the case in which the anemia

definitely decreased as the result of iron therapy. Data concerning this patient are given in chart 8. No history or evidence of bleeding could be obtained. This patient had confined himself to a milk diet for many months.

#### LIPIDS IN CHRONIC MYELOGENOUS LEUKEMIA AND CHLOROMA

Five cases of chronic myelogenous leukemia and one case of chloroma were studied. All of the patients were treated with arsenic by Dr. Claude E. Forkner, and he furnished the figures of the blood counts and the determinations of hemoglobin.

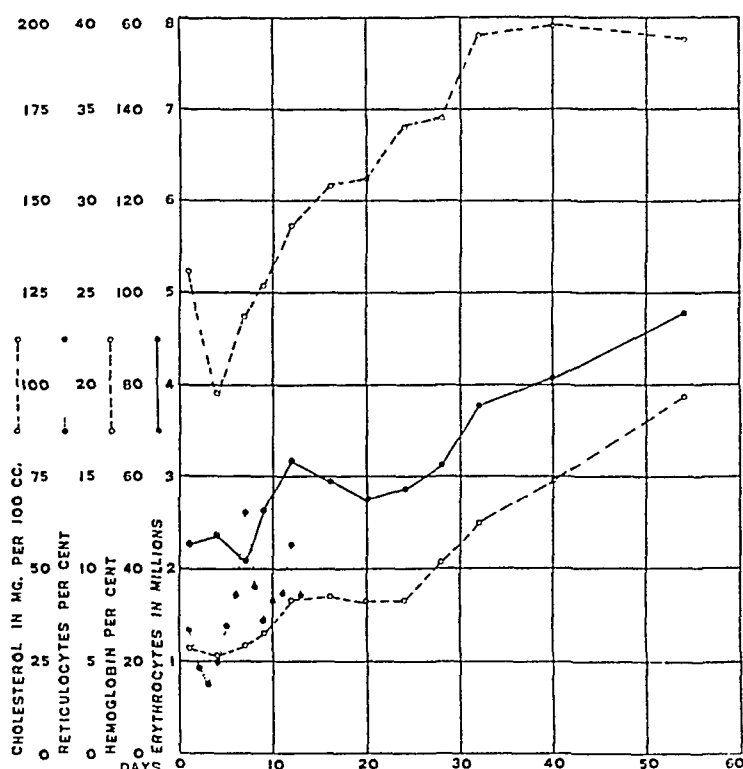


Chart 6.—Cholesterol in idiopathic hypochromic anemia with or without the association of a faulty diet. The relation of cholesterol to the reticulocyte response, red blood cells and hemoglobin. During the first month of observation, this patient had a slight fever (about 100 F. daily). The curve for the cholesterol is similar to the one obtained in cases of pernicious anemia after liver therapy.

The relationship between the red blood cell level and that of cholesterol is illustrated in chart 9 *A*. The striking fact is brought out that in chronic myelogenous leukemia there is a tendency toward sub-normal values of cholesterol, irrespective of whether or not there is anemia. Rarely was the value of cholesterol near the normal average. The lecithin phosphorus, on the other hand, did not show a value below normal (chart 9 *B*). Thus there is a definite dissociation between cholesterol and lecithin phosphorus in chronic myelogenous leukemia in contrast to the association found in various types of anemia.

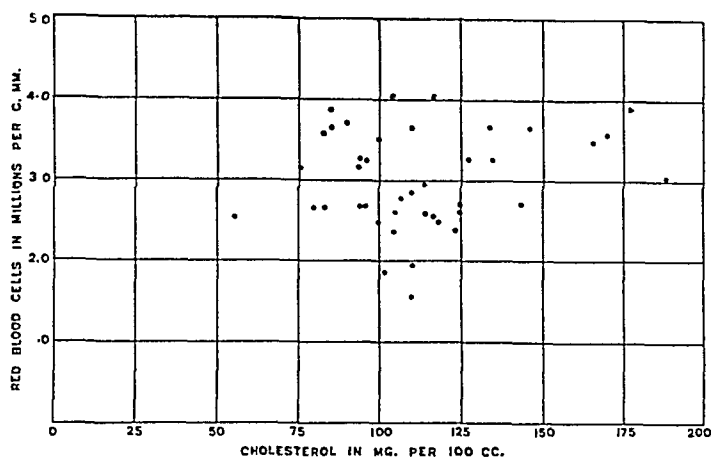


Chart 7.—Cholesterol in six cases of carcinoma of the stomach with anemia. Antianemic treatment influenced the red blood cells, hemoglobin and cholesterol but little, except in one case.

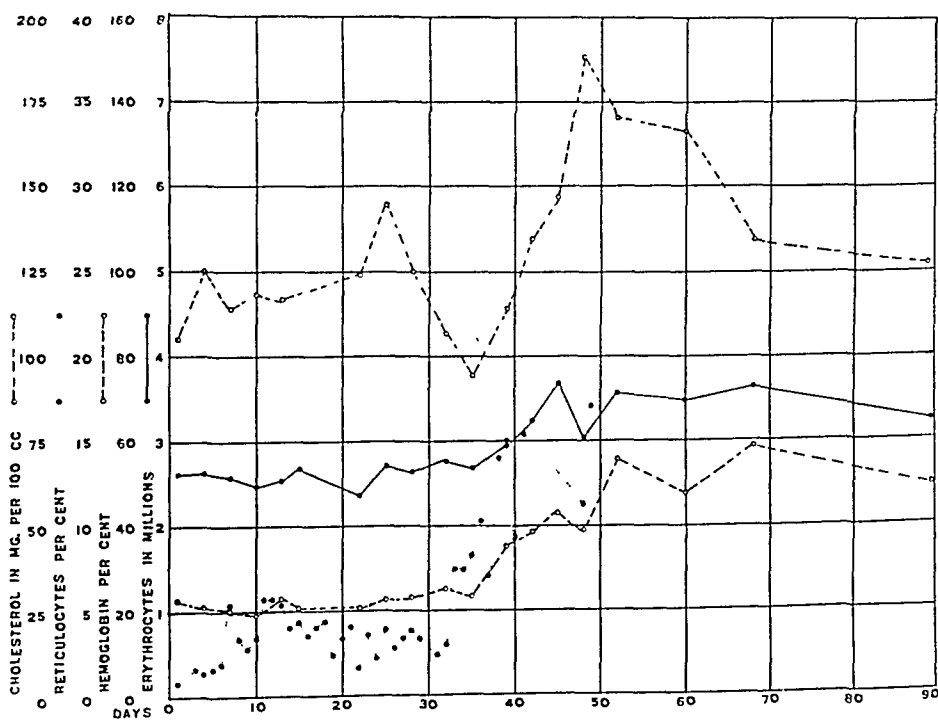


Chart 8.—The relation of cholesterol to the reticulocyte response, red blood cells and hemoglobin in one case of carcinoma of the stomach in which there was temporary improvement. Liver therapy for the first twenty-two days caused no improvement. Beginning on the thirtieth day, 6 Gm. of iron and ammonium citrate was administered daily. The patient responded with a marked increase of reticulocytes.

There was no positive correlation between the level of the plasma cholesterol and the basal metabolic rate or the number or type of white blood cells in the peripheral blood.

In the case of chloroma the anemia was severe, and both the lecithin phosphorus and the cholesterol were subnormal. The patient was observed only during the last two weeks of life, when he had a temperature varying daily from 99.5 to 104 F.

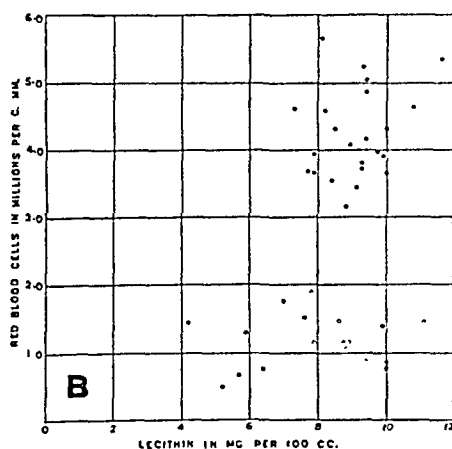
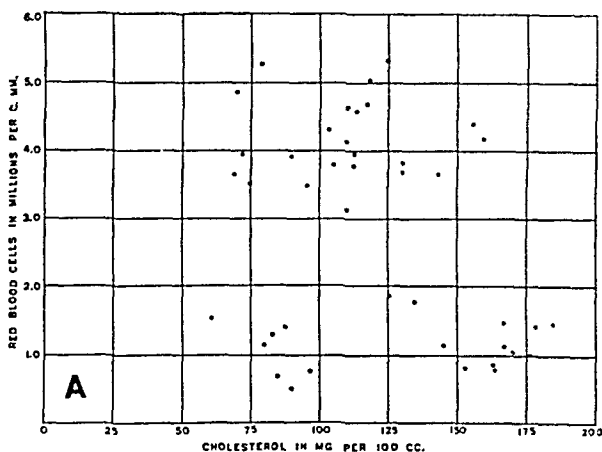


Chart 9.—*A*, cholesterol plotted against the red blood cells in myelogenous leukemia (●) and aplastic anemia (○). *B*, the relation of lecithin phosphorus to the red blood cells in myelogenous leukemia (●) and aplastic anemia (○). Note the dissociation of the levels of cholesterol and lecithin phosphorus in cases of myelogenous leukemia and the normal high values of cholesterol and lecithin phosphorus in cases of advanced aplastic anemia.

#### LIPOIDS IN APLASTIC ANEMIA

The findings in three cases of aplastic anemia were in sharp contrast to those in cases of chronic myelogenous leukemia. The differences are shown in chart 9, in which determinations of cholesterol and lecithin phosphorus have been plotted against the number of red blood cells for

the cases of aplastic anemia and of myelogenous leukemia. In spite of the severity of the anemia in the cases of aplastic anemia, both the cholesterol and the lecithin phosphorus, except as will be noted, remained within the upper limits of normal, in contrast to the lower levels in myelogenous leukemia, irrespective of anemia. In the cases of aplastic anemia yielding the lower figures for cholesterol the samples of blood were taken during fever induced by protein shock therapy or a transfusion of blood.

#### LIPOIDS IN MISCELLANEOUS TYPES OF ANEMIA

This group includes anemias of various origin. Facts about the eleven cases are given in table 3.

Of the three patients with splenic anemia, two had subnormal cholesterol and lecithin phosphorus, while in the third these constituents

TABLE 3.—*Rcd Blood Cells, Hemoglobin, Cholesterol and Lecithin Phosphorus in Miscellaneous Anemias*

Diagnosis	Sex	Age	Number of Determinations	Cholesterol, Mg. per Cc.	Lecithin Phosphorus, Mg. per Cc.	Red Blood Cells, Millions per C.Mm.	Hemoglobin, per Cent
Splenic anemia.....	♂	24	1	90	4.8	3.4	54
Splenic anemia.....	♂	65	1	117	6.0	4.2	90
Splenic anemia.....	♂	7	1	143	6.9	2.3	36
Pulmonary tuberculosis.....	♀	20	2	83-89	5.0-5.8	2.8-3.4	33-40
Nontropical sprue.....	♀	50	2	68-78	5.6-6.3	3.0-3.4	74-82
Osteomalacia.....	♀	38	1	88	...	3.9	71
Osteosclerotic anemia.....	♂	45	3	89-114	5.0-7.0	2.0-2.1	32-41
Hodgkin's disease.....	♂	48	1	91	7.4	3.0	55
Tuberculous adenitis.....	♀	52	1	121	10.7	4.3	60
Myxedema.....	♀	42	2	197-292	10.4-13.6	2.9-3.1	55
Myeloma with plasma cell anemia....	♀	38	1	163	7.4	2.3	41

were normal. In the latter case there had been a hemorrhage one week previously. Fever in the patient with pulmonary tuberculosis may have influenced the lipoids regardless of the anemia and the disease process. In the case of tuberculous adenitis without fever the lipid levels were normal.

Comments regarding the other cases are not necessary except as follows.

In the patient with myxedema with mild anemia, both cholesterol and lecithin phosphorus were above normal. With thyroid extract therapy the cholesterol decreased from 292 to 197 mg. per hundred cubic centimeters, and the lecithin phosphorus, from 13.6 to 10.4 mg. per hundred cubic centimeters in eight days.

#### COMMENT AND CONCLUSIONS

The lipid level in the blood plasma certainly does not bear any direct relation to the concentration of red blood cells or of hemoglobin.

Low values of cholesterol and lecithin phosphorus are not always found in severe hypochromic anemia, as has been claimed.<sup>5</sup> However, by frequent examination of the blood in the same patient and by analyzing the anemias of various types and causes, certain definite characteristics have been made out regarding the trends of the blood lipoids.

It has been pointed out that the lipoids behave differently in anemia due to chronic loss of blood and to that due to acute loss of blood, and that their increase following iron therapy in anemia caused by chronic loss of blood commences after the reticulocyte response, in contrast to an approximate paralleling of the reticulocyte reaction to liver therapy in pernicious anemia.

The observations permit the scanty data in the literature<sup>4c</sup> on the lipoids in anemia due to chronic loss of blood to be brought into line.

The normal range of lipoids with a tendency to hypercholesteremia and hyperlecithinemia in anemia due to acute loss of blood is of interest in connection with the observations of Feigl<sup>8</sup> immediately after acute hemorrhage and for a short period subsequently. He found a uniform increase of cholesterol in the blood under such circumstances, which was evident on the first day and marked forty-eight hours after the acute loss of blood. He noted that the hypercholesteremia persisted in a diminishing degree for more than a week. The rise was less marked in undernourished persons. Unfortunately, his report gives no data to indicate the severity of the anemia.

The cause of lipidemia after acute hemorrhage in man and in animals<sup>1</sup> has been variously interpreted. It is evident that it is not altogether due to a lack of red blood cells and decreased oxidation, as has been claimed by some investigators,<sup>9</sup> since an even greater lack of red blood cells is present in many anemias that show subnormal values of the blood lipoids. In acute hemorrhage there may be, however, a sudden decrease of lipase and a decrease of the metabolism of lipoids, as has been suggested by Horiuchi<sup>10</sup> and Sakai.<sup>11</sup> Bloor<sup>12</sup> considered that there was an outflow of lipoids into the blood in a greater quantity than the normal mechanism could dispose of at once, and in this outflow the displacement of fat by the blood-forming tissue may play an important part.

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8. Feigl, J.: Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden im Blute nach Blutentziehung, *Biochem. Ztschr.* **115**:63, 1921.

9. Boggs, T. R., and Morris, R. S.: Experimental Lipemia in Rabbits, *J. Exper. Med.* **2**:553, 1909.

10. Horiuchi, Y.: Studies on Blood Fat: II. Lipemia in Acute Anemia, *J. Biol. Chem.* **44**:363, 1920.

11. Sakai, S.: Zur Pathogenese der Lipämie, *Biochem. Ztschr.* **62**:387, 1914.

12. Bloor, W. R.: Lipemia, *J. Biol. Chem.* **49**:201, 1921.

Fishberg and Fishberg<sup>13</sup> have offered another explanation of the mechanism of the lipoidemia. They found that after a sudden loss of blood the total proteins were decreased, and that there was a shift in the albumin-globulin ratio in favor of the latter. They thought, therefore, that the increase of the lipoids after hemorrhage was due to the loss of serum proteins, and that the lipoidemia might be considered as a compensatory phenomenon, for the purpose of maintaining the colloidal osmotic pressure in the blood at a normal level. As confirmatory evidence of the foregoing hypothesis, Fishberg<sup>14</sup> showed that the osmotic pressure in lipemic blood is higher than in blood diluted to the same concentration of protein, and that this difference becomes apparent at the same time as the lipoids in the blood start to rise.

The reason for the low plasma cholesterol and lecithin in anemia caused by chronic loss of blood is not clear. Possibly there is merely a gradual depletion of the lipoids because of the constant loss of these substances from the body at a rate faster than they can be provided by the intake or the synthesis of food. On the other hand, it has been repeatedly shown<sup>1</sup> that low values of cholesterol may be obtained by increasing the functional activity of the reticulo-endothelial system, the main functioning part of the hematopoietic organs. During relapse in pernicious anemia it is highly probable that there is an increase in function of this system, and that this abnormal activity decreases as remission ensues. The relapse is accompanied by subnormal values of the lipoids, which increase promptly as remission begins. In anemia caused by chronic loss of blood the activity of the bone marrow is increased, as shown by the hyperplasia of the red blood cells. To account for the delayed rise of lipoids as compared with that in pernicious anemia, one must assume that an abnormal activity of the reticulo-endothelial system persists until the reticulocyte response to iron has subsided, since the lipoids do not increase until then. Whether or not such a correlation exists in anemia caused by chronic loss of blood can be determined only after material from the bone marrow, obtained by biopsy, has been studied at various stages. In anemia due to acute loss of blood there is also an increased activity of the hematopoietic organs with a rapid replacement of the fat in the bone marrow by cellular tissue. The possible relation of the lipoids to the activity of the hematopoietic organs may be obscured, however, as the cholesterol is mobilized in an effort to overcome the lowering of osmotic pressure caused by the sudden loss of plasma proteins.

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13. Fishberg, E. H., and Fishberg, A. M.: The Mechanism of the Lipemia of Bleeding, *Proc. Soc. Exper. Biol. & Med.* **25**:296, 1928; *Biochem. Ztschr.* **195**:20, 1928.

14. Fishberg, E. H.: Relations of the Serum Proteins and Lipoids to the Osmotic Pressure, *J. Biol. Chem.* **81**:205, 1929.

That there may be a possible relation of cholesterol to cell proliferation in the bone marrow is also suggested by the low cholesterol values we and other investigators<sup>1</sup> have found in chronic myelogenous leukemia. Kipp<sup>15</sup> observed that hypocholesteremia occurs also in acute infectious diseases like pneumonia, a disease in which there is a considerable production of white blood cells. He found that variation of cholesterol in the serum depended on the activity of the leukocytes.

The significance of the dissociation between cholesterol and lecithin phosphorus in chronic myelogenous leukemia is not clear. It has been assumed that lecithin phosphorus may possibly participate in the active formation of red blood cells, Sundstroem and Bloor<sup>16</sup> reported that in animals subjected to low barometric pressure there was a decrease of the lipid phosphorus in the blood. This they suggested might be due to an enrichment of the erythropoietic organs with lipid material, as the first phase of stimulation resulting from low barometric pressure. Whether lecithin phosphorus in the blood plasma is influenced by the proliferation of white blood cells is not known. The foregoing findings certainly suggest, however, that there is a definite dissociation between the two mechanisms controlling the level of cholesterol and lecithin in the blood stream. It appears as though the lecithin phosphorus in the plasma is not influenced by hyperplasia of the cells of the myelogenous series.

Two cases reported in the literature<sup>17</sup> with single determinations of the blood lipids corroborate our findings that in spite of severe anemia these elements may remain normal with a tendency to high figures in aplastic anemia, a condition in which the activity of the bone marrow is reduced to a minimum.

Considerable difference of opinion<sup>18</sup> has been expressed as to the relation of the cholesterol and lecithin level in the plasma and carcinoma. In the later stages of this disease there is a tendency for the lipoids to be lower than normal. In an analysis of fifteen cases of anemia associated with carcinoma recorded in the literature,<sup>1</sup> it was found that six patients had subnormal cholesterol values, and of these, all but one, in

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15. Kipp, H. A.: Variation in the Cholesterol Content of the Serum in Pneumonia, *J. Biol. Chem.* **44**:215, 1920.

16. Sundstroem, E. S., and Bloor, W. R.: The Physiological Effects of Short Exposures to Low Pressure, *J. Biol. Chem.* **45**:153, 1920.

17. Gibson, R. B., and Howard, C. P.: Metabolic Studies in Pernicious Anemia, *Arch. Int. Med.* **32**:1 (July) 1923. Antonelli, G.: Colesterinemia e resistenza globulare negli stati anemici, *Policlinico (sez. med.)* **21**:341, 1914.

18. Mattick, W. L., and Buchwald, K. W.: Blood Cholesterol Studies in Cancer: IV. Other Lipoid Partition, *J. Cancer Research* **13**:157, 1929. Klein, W., and Dinkin, L.: Beiträge zur Kenntnis der Lipoide des menschlichen Serums und zur Methodik der Lipoidbestimmung, *Ztschr. f. physiol. Chem.* **92**:302, 1914. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, *Arch. Int. Med.* **20**:599 (Oct.) 1917.



whom the location of the tumor was not stated, had carcinoma of the esophagus or the stomach. Our six patients with carcinoma of the stomach all had subnormal values. When the anemia can be lessened, the lipoids may increase, as in anemia caused by chronic loss of blood, as was shown in one of our cases.

In idiopathic hypochromic anemia and anemia associated with certain chronic dietary defects the distinguishing feature with regard to the level of the blood lipoids seems to be the lack of consistency. This may, however, be more apparent than real, and with further knowledge of the mechanisms of this sort of anemia, the lack of consistency may be explained. Patients, besides being treated with iron, were given an adequate diet, and although the anemia improved markedly, in most instances the lipoids remained uninfluenced. This indicates that the intake of food plays a subordinate rôle in whatever may be the mechanism that regulates the lipoids in the plasma. Histologically, the hematopoietic organs in these anemias show erythroblastic and normoblastic hyperplasia.<sup>19</sup>

Certain suggestive observations may be recorded. Thus protein shock and rise in temperature, conditions which can affect the reticulo-endothelial system, tended to lower the level of cholesterol and lecithin phosphorus in the blood. Hypothyroidism in the one case that we studied overshadowed any tendency toward hypocholesteremia that may exist in anemia. It is clearly evident<sup>1</sup> that conditions other than those recognized as affecting the hematopoietic organs, such as diabetes, nephritis or thyroid activity, may be associated with a disturbance of the level of cholesterol and lecithin in the blood plasma, but it is probable that there is a common mechanism. One may conclude, however, from the study of the cholesterol and lecithin phosphorus of the blood plasma in anemia that there seems to be some support for the hypothesis that the functional activity of the reticulo-endothelial system is intimately associated with controlling the level of the lipoids in the blood. The apparently contradictory results obtained in certain anemias may be explained satisfactorily with the elucidation of the exact functional state of the hematopoietic organs.

#### SUMMARY

The behavior of plasma cholesterol and lecithin phosphorus in sixty-one cases of anemia other than pernicious anemia has been determined and correlated with various factors.

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19. Weiner, W., and Kaznelson, P.: Ueber die zellige Zusammensetzung des Knochenmarkes nach Erfahrungen mittels der Sternalpunktion nach Seyfarth, *Folia haemat.* **32**:233, 1926. Dameshek, W.: Primary Hypochromic Anemia (Erythro-Normoblastic Anemia): A New Type of Idiopathic Anemia, *Am. J. M. Sc.* **182**:520, 1931.

The plasma lipoids were not related to anemia per se, as has been claimed, but definite characteristics were obtained in certain disorders of the blood. In anemia due to acute loss of blood the lipoids remained at normal levels or were high, while in that caused by chronic loss of blood they tended to be low at the height of the anemia, but increased with improvement after the reticulocyte response had subsided. This is in contrast to their behavior in pernicious anemia, in which the increase of the lipoids parallels the reticulocyte response.

In idiopathic hypochromic anemia with or without the association of a faulty diet, the chief characteristic of the course taken by the lipoids was the lack of consistency. In carcinoma of the stomach associated with anemia, the lipoids remained low except when the anemia decreased.

In chronic myelogenous leukemia, a dissociation between plasma cholesterol and lecithin phosphorus occurred. The level of cholesterol was found to be subnormal, or at the lower limit of normal, even when no anemia was present, while the lecithin phosphorus was normal. In aplastic anemia, on the other hand, the lipoids were high in spite of severe anemia.

# EFFECT ON THE REFLEXES OF THE CAROTID SINUS OF RAISING THE INTRACRANIAL PRESSURE

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MINNEAPOLIS

The work of Cushing<sup>1</sup> on intracranial pressure, published in 1902, brought out an important mechanism of adjustment in the body. He found experimentally that as intracranial pressure was gradually raised toward the level of the blood pressure, the blood pressure rose enough to keep ahead of it and to keep the brain sufficiently supplied with blood so that respiration continued. On the other hand, when intracranial pressure was raised suddenly, respiration would cease temporarily, following which the blood pressure would quite rapidly climb above the pressure of the cerebrospinal fluid, and respiration would begin again. Vagus effects, shown by slowing or stopping of the heart, were observed unless the intracranial pressure was increased very gradually and slowly. Meanwhile, by means of a window in the cranium of the dog, the pial vessels and the superior longitudinal sinus were observed. As the intracranial pressure was raised, increasing evidence of stasis and anemia was seen. As the pressure increased, the longitudinal sinus wavered, narrowed and thinned until it completely collapsed. At the equalization of pressures a marked blanching of the brain occurred. The blue veins in the sulci remained filled with blood. The arteries became very narrow; there was very little if any circulation between them. The centers were therefore poorly, if at all, supplied with blood. At this point death of the animal did not occur, as had been previously supposed, but the blood pressure rose sufficiently to overcome the high intracranial tension. The gyri became rosy again. Centers were once more nourished, and respiration, if it had ceased, began again. Thus circulation through the brain was reestablished. Cushing therefore concluded that the increase of the blood pressure was due to an anemia of the vasomotor area, just as the cessation of respiration was due to an anemia of the respiratory center when the cerebrospinal fluid pres-

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1. Cushing, H.: *Am. J. M. Sc.* **124**:375, 1902.

sure was too high. This work was confirmed by Eyster, Burrows and Essick.<sup>2</sup>

Since these experiments were performed, the influence of the carotid sinus has been discovered, and a considerable amount of work has been done on it. Since the work of Hering<sup>3</sup> and Heymans,<sup>4</sup> the "depressor" action of the sinus has been willingly conceded, but concerning its "pressor" action which results from an increase of blood pressure in the sinus there is some doubt. Some investigators, among whom are Danielopolu and co-workers,<sup>5</sup> Tomanek<sup>6</sup> and Schroeder,<sup>7</sup> held, and with apparently good evidence, that at least in higher mammals a pressor reflex can be elicited by direct pressure on the sinus. Thus the sinus may be like the sciatic nerve<sup>8</sup> in which either pressor or depressor reflexes may be elicited by stimulation at different frequencies.

There is a possibility that the carotid sinus played some part in Cushing's results. Thus, by increasing the resistance to the carotid flow, the increased intracranial pressure might elicit the direct pressor reflex of the sinus. The "vagus" effects spoken of by Cushing are also similar to those elicited by pressure in the neck, which, according to Heymans,<sup>9</sup> were noticed by Cooper in 1836, and by Morey in 1866, and, according to Cevolotto,<sup>10</sup> by Conato, in 1892. These effects from pressure in the neck have since been proved to have their origin in the carotid sinus. Also, if the carotid sinus plays a protective rôle to encephalic blood pressure, as Heymans and Bouckaert<sup>11</sup> suggested, should this protection not come into effect under conditions of increased intracranial pressure when the body is striving so hard to keep the blood pressure up to the necessary level? No work, as far as we know, has been done directly along these lines, but two different articles bear on the subject.

Heymans<sup>12</sup> studied the effect of increased intracranial pressure on the rate of the heart before and after denervation of the carotid sinus. A rise of intracranial pressure leads first to a slowing of the heart, then

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2. Eyster, J. A. E.; Burrows, M. T., and Essick, C. R.: *J. Exper. Med.* **11**:489, 1909.

3. Hering, H. E.: *Die Karotissinusreflexe auf Herz und Gefäße*, Dresden, Theodor Steinkopff, 1927.

4. Heymans, C.: *Le sinus carotidien et les autres zones vasosensibles réflexogènes*, Paris, Presses Universitaires de France, 1929.

5. Danielopolu, D.; Marcu, I., and Proca, G. G.: (a) *Klin. Wchnschr.* **6**:2339, 1927; (b) Aslan, A.; Marcu, I., and Proca, G. G.: *ibid.* **7**:408, 1928.

6. Tomanek, Z.: *Klin. Wchnschr.* **7**:898, 1928.

7. Schroeder, E.: *Klin. Wchnschr.* **6**:110, 1927.

8. Martin, E. G., and Mendenhall, W. L.: *Am. J. Physiol.* **38**:98, 1915.

9. Heymans, C.: *Rev. belge sc. méd.* **1**:507, 1929.

10. Cevolotto, G.: *Gior. med. d. Alto Adige* **1**:37, 1929.

11. Heymans, C., and Bouckaert, J. J.: *Compt. rend. Soc. de biol.* **99**:1871, 1928.

12. Heymans, C.: *Am. J. Physiol.* **85**:498, 1928.

to a short acceleration, followed in turn by a marked slowing. Heymans raised intracranial pressure before and after denervating the carotid sinus and got the same effects. He concluded that the action of increased intracranial pressure is entirely central, in contrast to the slowing of the heart due to increased cephalic blood pressure, an effect which originates in the carotid sinus. This conclusion, we believe, is not entirely justified, because he should have considered that the aortic depressor zones were still intact, and that they had been shown to be able to assume part of the tone of the carotid sinus after its extirpation.

Izquierdo<sup>13</sup> studied the influence of the aortic and carotid sinus reflexes on the height and form of the rise of blood pressure produced by peripheral stimulation of the splanchnic nerves. If one assumes, as did Cushing, that the rise of blood pressure following increased intracranial pressure is due to a direct stimulation of the vasomotor center, this effects the rise mainly by the action of the splanchnic nerves. Therefore, in this case, conditions are analogous to those in our experiments.

Izquierdo stimulated the splanchnic nerves peripherally with a faradic stimulus and found that when he extirpated all four depressor zones (the two carotid sinus and the two aortic depressor zones), the blood pressure rose very much higher, and the curve was much simpler than before. He found also, by varying the set which he eliminated first, that contrary to general opinion, the carotid sinus reflexes contributed most to this depressor effect; i. e., their extirpation helped the rise of blood pressure more than the extirpation of the aortic depressor zones. Izquierdo showed that the carotid sinuses are the main factors in producing the dip in the splanchnic pressure curve. He also found that if one carotid sinus was extirpated, there was usually a difference in rise of blood pressure, sometimes a considerable one. He showed that if all four depressor zones were present, their joint inhibitory action was so great, in some cases, that stimulation of the splanchnic nerves had little effect. He believed that when part of the depressors were eliminated, the others would assume their tone to a greater or less degree. Izquierdo concluded that the mechanism of the increased blood pressure on stimulation of the splanchnic nerves was a result of two factors: (1) a factor of direct vasomotor stimulation, and (2) an indirect (secondary) depressor factor due especially to the carotid sinuses.

Hering<sup>3</sup> and Koch<sup>14</sup> remarked that removal of some of these nerves regulating blood pressure has resulted in a more intense function of the

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13. Izquierdo, J. J.: *J. Physiol.* **70**:221, 1930.

14. Koch, E.: *Die reflektorische Selbststeuerung des Kreislaufes in Kisch*, Bruno: *Ergebnisse der Kreislaufforschung*, Dresden, Theodor Steinkopff, 1931.

remaining nerves. Cromer and Ivy<sup>15</sup> found that in dogs the physiologic rôle of the carotid sinus as a reflexogenic center for control of blood pressure can be readily taken over by other mechanisms.

#### EXPERIMENTS AND COMMENT

We have just completed a series of experiments on more than twenty dogs and rabbits, in which we used a somewhat modified combination of Cushing's and Hering's technics. We increased the cerebrospinal fluid pressure, at the same time varying the effect of the carotid sinus either by stimulation or by extirpation. Ether anesthesia with premedication by morphine was usually used, although the same results were obtained when ethylcarbonate (urethane) or phenobarbital sodium was used.

The apparatus was as follows: One arm of a specially constructed T-shaped metal cannula was introduced into the subarachnoid space, usually over the parietal area of the skull to minimize bleeding. This was screwed tightly into the trephine hole and thus kept air-tight. To the second arm of the "T" was attached a hose for flushing, this outlet being closed off with a clamp during the experiment. To the other arm was attached a long rubber hose running to a pressure bottle suspended on a pulley above the table. A side arm on this hose was connected to a mercury manometer which recorded the intracranial pressure on a kymograph.

The fluid used in the pressure bottle was an isotonic 0.9 per cent solution of sodium chloride which was kept at approximately 38 C. to avoid shock to the animal. The bottle was corked tightly, but the outlet at the bottom was left open, allowing the fluid to exert its pressure continuously on the contents of the subarachnoid space.

In the beginning of the experiment, the level of the fluid in the bottle was brought to the same height as the subarachnoid space of the dog, and the needle which recorded intracranial pressure was set at zero. Thus, to be more accurate, there would have to be added to our readings a figure corresponding to the normal intracranial pressure of the dog, which when taken with the dog lying down is much too small to be measured by the apparatus.

The cerebrospinal fluid pressure could then be increased up to a certain point by elevating the bottle on a pulley. If higher pressures were desired, the tension was further increased by pumping air over the fluid of the closed bottle, the bulb of an ordinary sphygmomanometer being used. The manometer needle writing this pressure on the drum recorded any changes in intracranial pressure.

Blood pressure was recorded from the femoral artery by cannulating it and connecting the cannula to a mercury manometer by a rubber tube. Respirations were recorded by a lever connected to a tambour strapped to the animal's chest. A stimulation recorder which was regulated by a foot pedal allowed the exact time of a manipulation to be recorded. Time was recorded usually in half minute intervals. All of these writing points were set in the same ordinate on the graph so that simultaneous readings could be obtained.

Before proceeding with the experiment, we isolated the carotid sinuses in the neck according to Hering's technic. A midline incision was made. The common carotid arteries were shelled out from below upward, and the internal and external

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15. Cromer, S. P., and Ivy, A. C.: *Proc. Soc. Exper. Biol. & Med.* **28**:565, 1931.

carotids were separated from surrounding structures, care being taken to avoid injury to the numerous fine arteries and nerves in this region. One or two of the smaller vessels near the sinus were tied off in order to expose the sinus more completely. A thread around the external carotid allowed the sinus to be moved with no stimulation during the experiment.

Dry gauze was used to insulate the sinus from other structures during stimulation. Special care was taken to avoid unnecessary shock, and time was always allowed after manipulation for the animal's nervous system to recover. In certain cases we isolated the nerves, by either cutting or stimulating them according to Hering's technic.

The carotid sinuses were first stimulated both electrically and mechanically to prove that they were intact and working normally, and to see how much reaction the individual animal gave.

Intracranial pressure was then increased by introducing the warm physiologic solution of sodium chloride into the cerebrospinal space by increasing the pressure in the bottle. Usually the pressure was increased in stages. In most experiments it was increased gradually, although sudden changes were occasionally used for comparison. The rapidity of change was found to make very little difference, except for the fact that the more gradual change avoided most of the effects described by Cushing as vagal.

On raising intracranial pressure with the carotid sinuses intact, we observed much the same results as did Cushing. When the intracranial pressure was raised, the blood pressure rose, and in some cases, the needle used to test the blood pressure was pushed above the limits of our recording apparatus without any signs of failure (over 350 mm.). The height to which the blood pressure could be raised in this way evidently depended on the individual reaction of the dog, the extent of shock and the degree of anesthesia. In some dogs the blood pressure would fail quite soon, that is, climb a short distance and suddenly fall rapidly, following which the animal would die of respiratory failure unless the intracranial pressure was immediately lowered and artificial respiration instituted. On lowering the intracranial pressure toward normal, the reverse effect, a lowering of blood pressure, was observed. Chart 2 *A* presents the records for an animal in which such effects were obtained.

Our main experiments, however, were in testing the responses of the carotid sinus during this increased cerebrospinal fluid pressure. When the intracranial pressure was at different levels, that is, below, on a level with, or above blood pressure, the carotid sinuses were stimulated, either electrically or mechanically. When this was done, even if the intracranial pressure was greater than the blood pressure, stimulation of the sinus always produced a fall of blood pressure. This fall of pressure was usually greater than that which would occur under normal conditions of intracranial pressure.

In chart 1 the intracranial pressure had been raised above the blood pressure, but before the blood pressure responded, the carotid sinus was stimulated electrically. The blood pressure went down much more

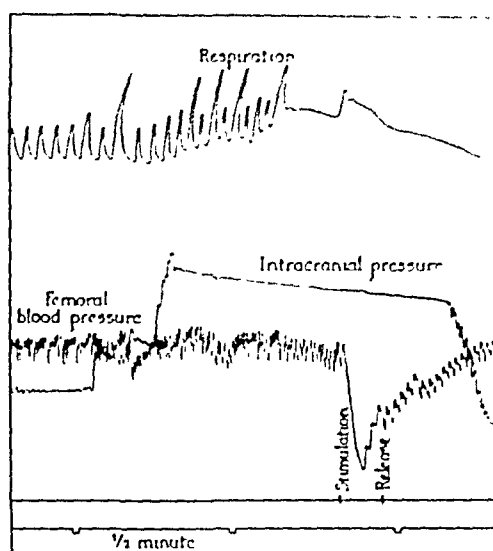


Chart 1.—Stimulation of the left carotid sinus under increased intracranial pressure.

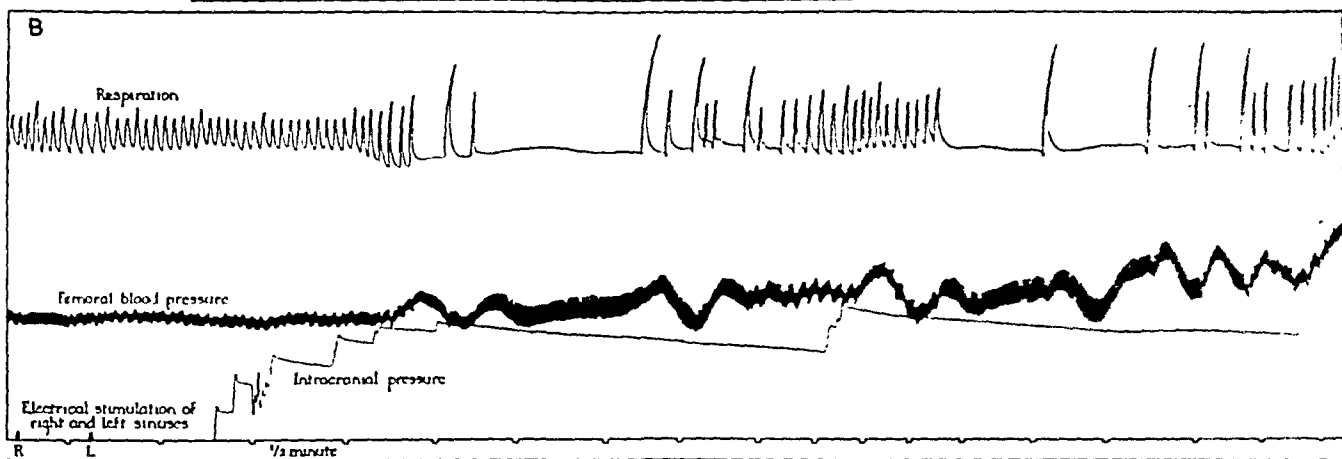
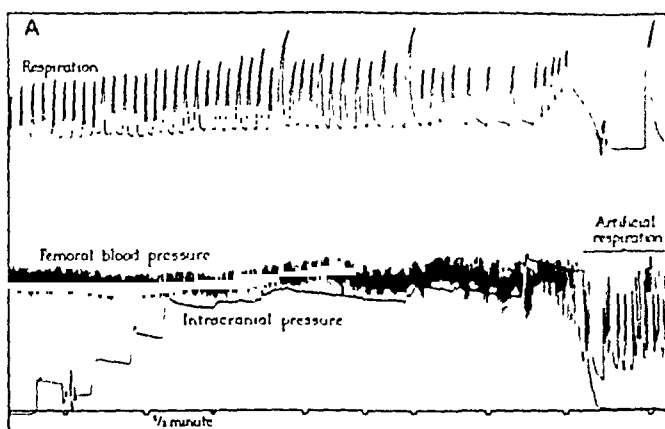


Chart 2.—*A*, showing the weakness of response and the early failure of the blood pressure when both sinuses are intact; *B*, showing greater response and no failure of the blood pressure when both sinuses are denervated; same animal as in *A*.



than it had before with the same intensity of stimulation when the intracranial pressure was normal. The same result occurred almost constantly with increased intracranial pressure, even when this was considerably below the level of the blood pressure.

The experiments of raising intracranial pressure after denervation of the sinuses were even more conclusive. In these experiments, a graph of the effect of increased intracranial pressure was made in the usual way. The carotid sinuses were denervated thoroughly in the following manner. Hering's nerve, if found, was cut, and the artery was stripped of all excess tissue and carefully painted with 5 per cent

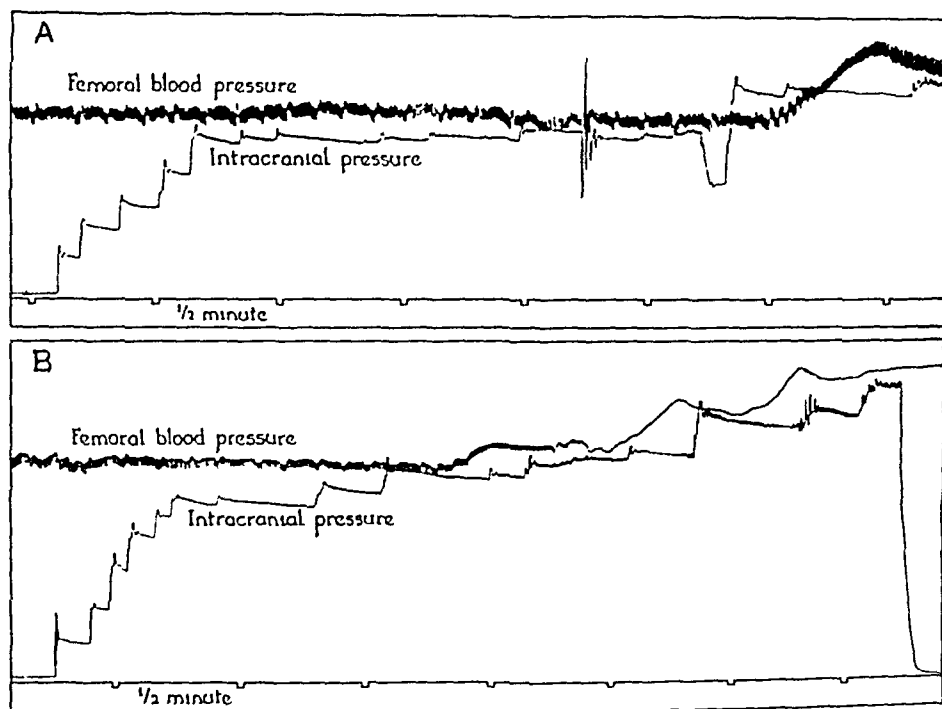


Chart 3.—*A*, showing the weakness of the response of blood pressure when both sinuses are intact. *B*, same animal as in *A*; the results when both common carotid sinuses are clamped off.

phenol. After allowing time for the shock to wear off, we repeatedly stimulated the carotid sinus with a strong electrical current. If we could get no effect either on respiration or on blood pressure, we believed our denervation was complete and proceeded with the experiment.

Then, when the reflexes of the carotid sinus were destroyed, we repeated the raising of intracranial pressure in the same manner as when they were intact. In practically every case, the rise of blood pressure was greater than before (chart 2 *B* and 3 *B*). In no case was the response less, although the animal was of course in poorer condition than previously.

The blood pressure rose more promptly and to greater height after the intracranial pressure had approached it than before denervation occurred, and failure of the vasomotor mechanism did not appear to occur as early. The blood pressure also went up before the intracranial pressure approached as closely to it as it did earlier, when the sinuses were intact.

Chart 2 shows a representative experiment of this type. In 2*A* is shown the very weak and feeble action of the blood pressure in overcoming intracranial pressure. In fact, the intracranial pressure had to be raised above the blood pressure before the latter would rise. The blood pressure rose very little before the vasomotor center failed, and then the blood pressure fell rapidly. Immediate lowering of the intracranial pressure and artificial respiration were necessary to save the animal's life. On the same dog (chart 2*B*), however, after denervating the carotid sinuses, the blood pressure went up much more easily and did not fall so soon, and a greater difference between these two pressures was maintained. After the intracranial pressure had been lowered and had remained at normal for some time, the carotid sinuses were again stimulated to make sure of their denervation.

These results remind one of Izquierdo's findings. He found that in some cases the depressor action was so strong that very little increase of blood pressure resulted from stimulation of the splanchnic nerves. Eyster, Burrows and Essick remarked that in some of their animals very little increase of blood pressure resulted from increased intracranial pressure and early failure was seen.

In other experiments we shut off the common carotids below the carotid sinuses. The results were the same as when the carotid sinuses were eliminated by the method of denervation. This is illustrated by chart 3*A* and *B*. The response of the blood pressure is somewhat better to start with than in chart 2.

The same experiments were performed on three rabbits. In addition to denervation of the sinuses, the depressor nerves in the neck were also cut. The difference before and after denervation of these four depressor areas was not very great, but always, as in the dogs, the response tended to be better than before denervation. The responses, however, even in normal rabbits, were not so satisfactory or so conclusive as in dogs.

These results, which in our series were quite constant, lead us to believe that the carotid sinus is not primarily concerned with the mechanism described by Cushing; his conclusion that the mechanism is a central one, probably effected by anemia of the medullary centers, seems to hold true. The carotid sinuses as well as the aortic depressor areas must act secondarily on the centrally increased blood pressure and tend to lower it. It is striking that, although the differences we found

before and after the denervation of these depressor zones were, in some cases especially, not great, they were always in the same direction, the response tending to be better after these brakes were out of the way. In other words, in these experiments the blood pressure acts much the same as in Izquierdo's experiments, except that in our experiments the vessels were constricted by the increased intracranial pressure (anemia) stimulating the centers, while in Izquierdo's experiment the constriction was due to electrical stimulation of the splanchnic nerves. The increased intracranial pressures have little if any direct effect on the reflexes of the carotid sinuses, which tend to inhibit the vasomotor and respiratory centers and stimulate the cardio-inhibitory center. All of these effects are produced when the blood pressure begins to rise in the normal animal and work against the rise of pressure necessary to supply the brain with blood. One might expect a greater difference in effect after elimination of the sinuses than was actually found, but in the dogs the aortic depressors were still present, and rabbits do not stand the severe operation and long anesthesia very well. In our experiments, we found no evidence that the sinuses ever act as pressor mechanisms and thus help the centers receive the blood they need. The anemia of the centers is the stronger and more fundamental condition and overcomes the secondary depressor reflexes caused by the rise of pressure. These secondary reflexes are sometimes nearly able to overcome the primary effects.

Although in lower animals only depressor effects have been found from stimulation of the sinus by pressure, in man and apes, pressor effects have been obtained<sup>5</sup> in certain cases from such stimulation. It has been suggested that these pressor results might have been due to pressing on the carotid artery below the sinus, which thus lowered the pressure in the sinus. We do not think this is the true explanation, as the levels of stimulation were varied.<sup>5a</sup> We believe the evidence points to the fact that the sinus in man and apes is, as Danielopolu<sup>5b</sup> puts it, amphoteric. It may be analogous to a peripheral nerve in cases in which it has been shown<sup>8</sup> that pressor, depressor or mixed results can be produced by altering the strength and the rhythm of the stimulus. In our experiments, even though an emergency existed, no evidence of a pressor effect was found. There is a certain amount of evidence that in dogs very low pressures may actually stimulate pressor mechanism and not merely produce its effect from a dropping out of the depressor mechanism. No one seems to have found that this pressor mechanism was stimulated by high pressures, as may happen in man and apes.

In doing these experiments, we made a number of incidental observations. The first striking thing we noticed was how close the intra-

cranial tension could be brought to the mean blood pressure before a rise of blood pressure resulted. Tzanck and Renault<sup>16</sup> stated their belief that the venous pressure and the cerebrospinal fluid pressure are almost the same, the latter varying with the former. Consequently, it is interesting to note how small a difference could exist between arterial pressure and venous pressure before sufficient anemia of the medullary centers resulted to cause a cessation of respiration or an increase of blood pressure. This difference seemed to increase after extirpation of the carotid sinuses. In most animals these centers seem to be able

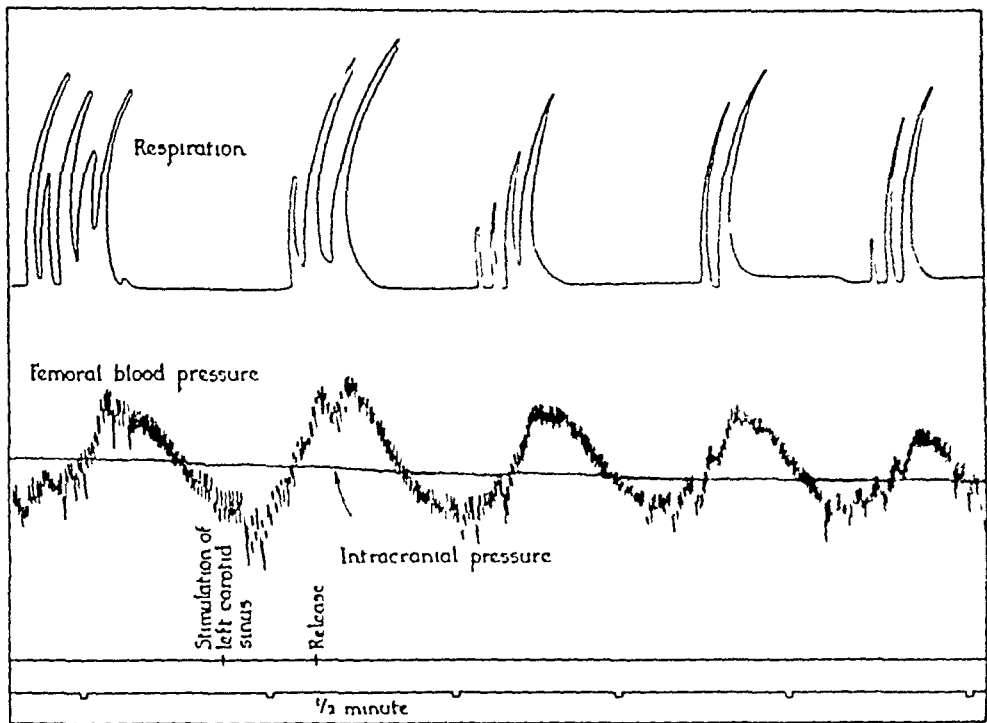


Chart 4.—The Traube-Hering waves and the Cheyne-Stokes respiration under increased intracranial pressure.

to get along with a very poor supply of blood provided the blood is properly arterialized.

Another observation was the great variability shown by different animals both as to the increased intracranial pressure and as to the carotid stimulation. Some could stand increases of intracranial pressure many times the original value, while in others the vasomotor mechanism collapsed very readily. This, of course, was influenced by the condition of the animal and the anesthesia.

As Cushing found, sometimes very prominent Traube-Hering waves and Cheyne-Stokes respiration resulted. Cushing explains these as being due to a poor condition of the respiratory center, which in this case

16. Tzanck, A., and Renault, P.: *Compt. rend. Soc. de biol.* **96**:157, 1927.

would be caused by lack of nourishment due to the increased intracranial pressure. In some cases, the high point of the blood pressure would be above the intracranial pressure and the low point below the intracranial pressure, and as a result, Cheyne-Stokes respiration would result, the hyperpnea occurring when the blood pressure was above the intracranial pressure and the apnea when it was below, as shown in chart 4.

On some of our graphs the curve for intracranial pressure showed marked oscillations of the same spacing as those of respiration. This increase in expiration and decrease in inspiration of intracranial pressure has been noted by others before (Cushing<sup>1</sup> and Golla and Symes<sup>17</sup>). Cushing explains it by pulsation of the brain, which, he says, is greater the higher the intracranial pressure.

In these experiments we took the opportunity to verify some of the results on the carotid sinus which many investigators have obtained. On simple stimulation of the sinus we got the typical depressor effect: slowing of the heart and respiration with a fall in blood pressure. What was peculiar to us was that in some dogs the blood pressure effect was pronounced and the respiratory effect slight, while in others the reverse held true.

#### CONCLUSIONS

1. The rise of arterial pressure following an increase of intracranial pressure is, in dogs and rabbits, of central origin, as Cushing thought, and does not start in the carotid sinus. In our experiments the carotid sinus was always found to act as a depressor zone tending to keep the pressure down even when the centers needed blood.

2. Following denervation of the sinus, increased intracranial pressure caused a more prompt and greater rise of arterial pressure. The differences before and after denervation were not very great, and the same was true in rabbits in which the influences of the aortic depressors also were removed.

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17. Golla, F. L., and Symes, W. L.: *J. Physiol.* **50**:32, 1916.

# ABSORPTION OF DEXTROSE BY RECTUM

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A recent paper by Scott and Zweighaft<sup>1</sup> has again raised a long-standing controversy on the question of the absorption of dextrose by rectum. They have demonstrated in a series of studies on fifty medical students that there is no evidence of the absorption of dextrose when it is given in a 10 per cent concentration (40 Gm.). The literature disclosed a marked difference of opinion regarding the absorbability of dextrose administered by this route. In view of the therapeutic importance of the answer to this question, the authors have attempted an investigation of this problem in an unselected series of diabetic and nondiabetic patients in a hospital ward.

The following investigators found evidence that dextrose is absorbed when it is instilled into the rectum. Schoenborn<sup>2</sup> showed that there was a maximum absorption of dextrose in from one to two hours. Von Leube<sup>3</sup> found 63 out of 70 Gm. absorbed, mostly in one hour. Müller<sup>4</sup> obtained an absorption of 50 per cent of the amount instilled in two hours. Reach<sup>5</sup> was one of the earliest investigators to demonstrate a rise in the respiratory quotient after the rectal instillation of dextrose, and he concluded that there is a slight absorption. Others who found an elevation in the respiratory quotient and confirmed Reach's observations were Bergmark,<sup>6</sup> Hári and von Halász,<sup>7</sup> Fleming<sup>8</sup> and Car-

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From the Medical Service of Dr. J. N. Cohen and the Laboratories of the Greenpoint Hospital.

1. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following the Rectal Administration of Dextrose. *Arch. Int. Med.* **49**:221 (Feb.) 1932.

2. Schoenborn: *Zur Frage der Resorption von Kohlehydraten im menschlichen Rectum*, Dissert., Würzburg, 1897.

3. von Leube, in Leyden: *Handbuch der Ernährungstherapie und Diätetik*, Leipzig, Georg Thieme, 1903, vol. 1, 496.

4. Müller: *Verhandl. d. Kongr. f. inn. Med.*, 1898, p. 454.

5. Reach: *Arch. f. exper. Path. u. Pharmacol.* **47**:231, 1902.

6. Bergmark: *Skandinav. Arch. f. Physiol.* **32**:335, 1915.

7. Hári, P., and von Halász, A.: *Die Therapie des Diabetes mellitus mit Zuckerklystieren*, Dissert., Kiel, 1917.

8. Fleming: *J. Physiol.* **53**:236, 1919.

penter.<sup>9</sup> Deucher,<sup>10</sup> Zemisch,<sup>11</sup> Stölting,<sup>12</sup> Hausmann,<sup>13</sup> Orłowski<sup>14</sup> and Bergmark<sup>6</sup> reported that the absorption of dextrose varied from 50 to 89 per cent of the amount introduced. Von Halász<sup>15</sup> obtained marked absorption, especially when the dextrose was given in high concentration. Satta<sup>16</sup> attempted to prevent diabetic acidosis with the administration of dextrose rectally, and he maintained that he was successful. Hubbard and Wilson<sup>17</sup> obtained sufficient absorption to decrease the excretion of acetone following a diet high in fat content. Lüthje<sup>18</sup> obtained marked absorption, and he demonstrated a rise in blood sugar. Tallerman<sup>19</sup> gave 60 Gm. in 180 cc. of a saline solution. He found a maximum rise of blood sugar of 62 mg., with an average of 19 mg., and he concluded that some dextrose is absorbed. Levi<sup>20</sup> confirmed Tallerman's observations, but stated that there is a slight and slow absorption. He did not analyze the return of the enema. Julesz and Winkler<sup>21</sup> showed that hyperglycemia occurred twenty minutes after 500 cc. of a 20 per cent solution of dextrose was given to normal subjects.

Among those who were unable to demonstrate evidence of absorption were Rosenfeld,<sup>22</sup> Janson-Blohm<sup>23</sup> and Rubino and Varela.<sup>24</sup> Pressman<sup>25</sup> studied this problem in seven human subjects. He administered 240 cc. of a 30 per cent solution of dextrose and found that the blood sugar was at or below the fasting level ninety minutes later. He recovered 24 per cent after four hours. He maintained that a large

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9. Carpenter, T. M.: *Human Metabolism with Enemata of Alcohol, Dextrose and Levulose*, Washington, D. C., Carnegie Institution, 1925.

10. Deucher: *Cor.-Bl. f. schweiz. Aertze* **33**:41, 1903.

11. Zemisch: *Ausnutzung von Nährklystieren*, Halle, 1903.

12. Stölting: *Ueber den Wert verschiedener Zuckerarten als Bestandteil von Nährklystieren*, Dissert., Halle, 1904.

13. Hausmann: *Experimentelle Untersuchungen über die Ausnutzung verschiedener zusammengesetzter Zuckerclysmen*, Dissert., Halle, 1905.

14. Orłowski: *Ztschr. f. diätet. u. physik. Therap.* **8**:481, 1905.

15. von Halász: *Deutsches Arch. f. klin. Med.* **98**:433, 1910.

16. Satta: *Beitr. z. chem. Physiol. u. Path.* **6**:376, 1905.

17. Hubbard and Wilson: *Proc. Soc. Exper. Biol. & Med.* **19**:292, 1922.

18. Lüthje, H.: *Therap. d. Gegenw.* **54**:193, 1913.

19. Tallerman, K. H.: *Quart. J. Med.* **13**:356, 1920.

20. Levi, D.: *Brit. J. Surg.* **15**:282, 1927.

21. Julesz and Winkler: *Ztschr. f. d. ges. exper. Med.* **80**:823, 1932.

22. Rosenfeld: *Berl. klin. Wchnschr.* **44**:1663, 1907.

23. Janson-Blohm: *Upsala läkaref. förh.* **20**:331, 1915.

24. Rubino and Varela: *Klin. Wchnschr.* **1**:2370, 1922.

25. Pressman, J.: *Am. J. M. Sc.* **179**:520, 1930.

At the end of two hours the patients were given an enema with 500 cc. of tap water, and the evacuation was collected. These returns were analyzed for the dextrose content by the Benedict quantitative method for estimations of sugar in the urine.

## RESULTS

The accompanying table is a composite picture of the effect of the rectal administration of dextrose on the blood sugar, and it also indicates the percentage of sugar absorbed. The cases are grouped accord-

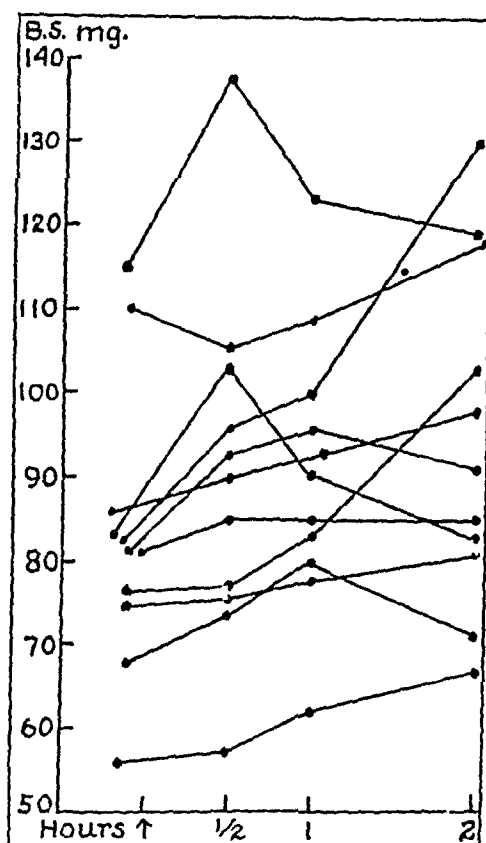


Chart 1.—Results of the administration of dextrose in nondiabetic patients; 250 cc. of a 10 per cent solution of dextrose (25 Gm.) was administered by rectum. The average amount of blood sugar recovered was 6.8 Gm.

ing to the amount and concentration of dextrose given. The upper part of the table shows the results in nondiabetic persons, while the lower part contains the study on diabetic patients. One observes that in the nondiabetic group there is a rise in the blood sugar ranging between 16 and 25 per cent, and that the amount of dextrose recovered at the end of the experiment varies between 10 and 27 per cent at the end of two hours. This indicates that as much as 90 per cent of the dextrose administered by rectum was absorbed. In the diabetic group, much the same picture prevails, except for the fact that two patients showed no rise in blood sugar, and one even experienced a 20 per cent



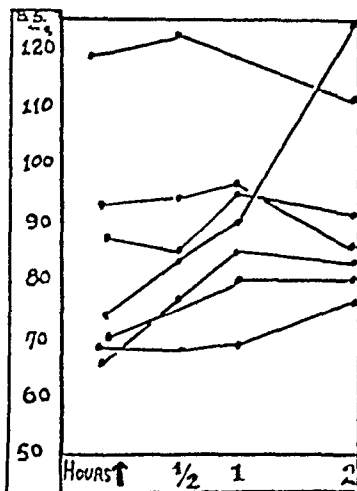


Chart 2

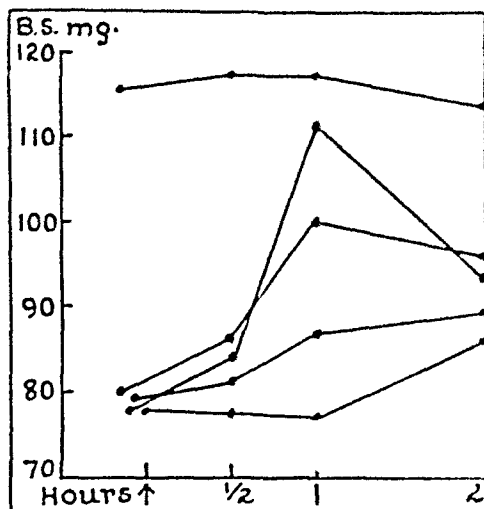


Chart 3

Chart 2.—Results in nondiabetic patients in whom 200 cc. of a 25 per cent solution of dextrose (50 Gm.) was administered by rectum. The average amount of blood sugar recovered was 9.2 Gm.

Chart 3.—Results in nondiabetic patients in whom 400 cc. of 5 per cent solution of dextrose (20 Gm.) was administered by rectum. The average amount of blood sugar recovered was 2.1 Gm.

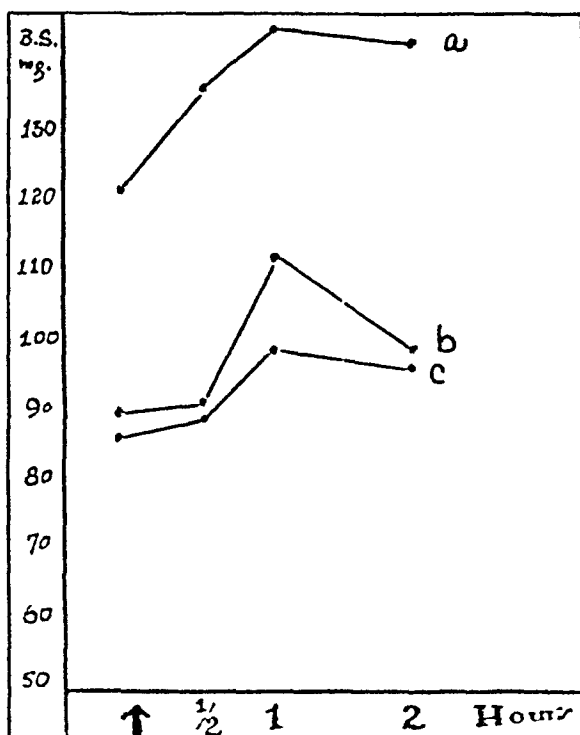


Chart 4.—Results in nondiabetic patients: (a) given 200 cc. of a 5 per cent solution of dextrose (10 Gm.); recovered, 0.8 Gm.; (b) given 200 cc. of a 50 per cent solution of dextrose (100 Gm.); recovered, 18.3 Gm.; (c) given 200 cc. of a 5 per cent solution of dextrose (100 Gm.); recovered, 0.0 Gm.

depression. The other four diabetic patients had elevations in the blood sugar of 9, 21, 38 and 50 per cent. All, however, showed evidence of absorption by the analysis of the rectal return. In the patient in whom there was a depression in the blood sugar, only 14 per cent of the amount administered could be recovered at the end of two hours.

Chart 1 is a graphic representation of the results in the nondiabetic persons who received 250 cc. of a 10 per cent solution of dextrose

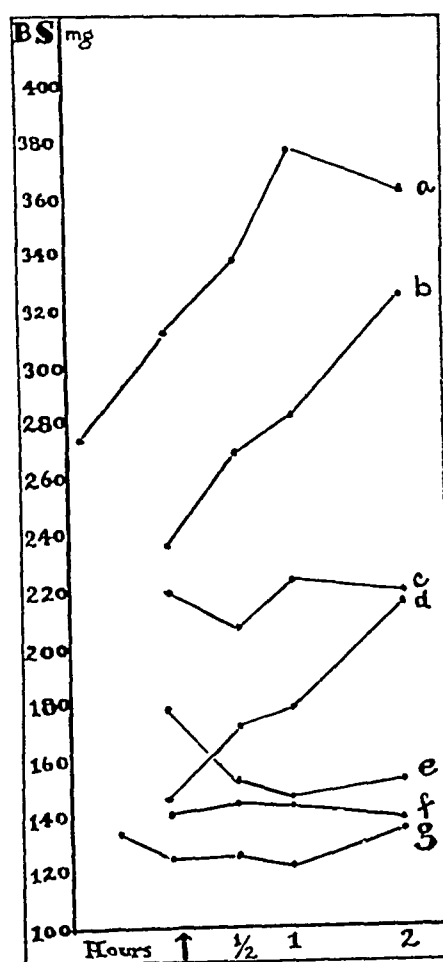


Chart 5.—The results of the administration of dextrose solution in diabetic persons are as follows: (a) with 250 cc. of a 10 per cent solution of dextrose (25 Gm.) administered, 9.4 Gm. of blood sugar was recovered; (b) with 400 cc. of a 5 per cent solution of dextrose (20 Gm.), 2.7 Gm.; (c) with 200 cc. of a 25 per cent solution of dextrose (50 Gm.), 9.0 Gm.; (d) with 400 cc. of a 5 per cent solution of dextrose (20 Gm.), 1.2 Gm.; (e) with 400 cc. of a 5 per cent solution of dextrose (20 Gm.), 2.7 Gm.; (f) with 200 cc. of a 25 per cent solution of dextrose (50 Gm.), 6.0 Gm., and (g) with 250 cc. of a 10 per cent solution of dextrose (25 Gm.), 10.2 Gm.

(25 Gm.). One observes a general tendency for the curves to rise; some rise at the end of thirty minutes, but most of them show a delayed rise,

reaching the maximum level at the end of two hours. Chart 2 shows the delayed rise with 200 cc. of a 25 per cent solution of dextrose (50 Gm.). Chart 3 shows a similar phenomenon with 400 cc. of a 5 per cent solution of dextrose (20 Gm.). Chart 4 shows the results in a patient who received 200 cc. of a 50 per cent solution of dextrose (100 Gm.) and in two patients who were given 200 cc. of a solution of dextrose (10 Gm.). All of the patients showed the same general tendency. Chart 5 is a graphic summary of the studies made with diabetic patients. Three show no rise and four a delayed elevation.

#### COMMENT

The purpose of this investigation was to determine, in the face of complicating opinions, whether or not dextrose can be absorbed by rectum. We were not particularly interested to know whether absorption, if it did occur, was equal in rate and degree to that occurring when dextrose was given by the oral route. It was important to determine whether a patient to whom dextrose could not be administered orally and for whom the parenteral route was contraindicated could derive the benefits of dextrose when it was in contact with the large bowel. This question is one of therapeutic importance and requires a definite answer. The literature discloses evidence that there is an elevation in the respiratory quotient following the rectal administration of dextrose and clearly indicates that dextrose given in this manner was not only absorbed but utilized.

Pressman's statement that the dextrose not accounted for in the enema return at the end of the experiment could have undergone bacterial fermentation cannot be accepted by us. While he maintains that 34 per cent of the dextrose can disappear by fermentation with feces in five hours, we found that in one patient who evacuated the dextrose enema at the end of one hour only 8 to 25 Gm. given was returned, indicating that 68 per cent was not accounted for in an hour. This period was not long enough to allow for fermentation. It also cannot account for the disappearance of as much as 90 per cent of the dextrose in two hours.

Further evidence that dextrose is absorbed in significant quantities is illustrated by the fact that a diabetic patient who had recently experienced an attack of hypoglycemia as the result of an overdosage of insulin was immediately relieved by the administration of 25 Gm. of dextrose by rectum. Dextrose was given in this manner by the interns because the patient's jaw was rigid from the tetanic syndrome asso-

ciated with a state of hypoglycemia, and he found considerable difficulty in inserting the needle into a vein, making it necessary to administer the dextrose by rectum.

#### CONCLUSIONS

1. Dextrose is absorbed when it is administered by rectum.
2. Although dextrose does not pass through the membrane of the colon as rapidly as through the small intestine, a sufficient amount is absorbed to warrant recognition of this method as an acceptable therapeutic procedure.

9 Prospect Park West.

absent. Over the area of dulness in the left axilla a friction rub was detected. On percussion, the heart was not found to be increased in size. The first sound, at the apex, was snapping in character; the second sound, over the pulmonic area, was accentuated; a short systolic murmur was heard just inside the heart's apex. Physical examination revealed no other abnormality.

On the sixth day after entry, the temperature reached normal. The signs and symptoms referable to the chest gradually decreased with the fall in temperature. Salicylates were not given until after the cessation of fever and the disappearance of signs in the chest. The patient remained asymptomatic. A blowing diastolic murmur over the base of the heart was heard during the last two weeks of the four weeks in the hospital. Roentgenologic studies at the time of entry showed fine mottling throughout the pulmonary fields but no evidence of fluid at the base of either lung. The heart showed a mitral deformity. Later studies showed the pulmonary fields to be clear. Electrocardiographic studies showed the QRS complex to be slurred and the T waves to be flat in all leads. The leukocyte count was 20,200 per cubic millimeter at the time of admission, and 8,100 at the time of discharge. The urine was normal. Examinations of the sputum gave repeatedly negative results for tubercle bacilli.

The case was one of recurrence of rheumatic fever, with unilateral fibrinous pleurisy accompanied by evidence of pulmonary changes.

The clinical pictures in cases 2 and 3, in which unilateral fibrinous pleurisy occurred during the course of a recurrence of the acute manifestations of rheumatic fever, were similar. The extension of the process to the pleura was accompanied by sharp, stabbing pain in the chest, which was increased on movement of the wall of the chest, and by the presence of a pleural friction rub. The duration of the signs and symptoms was relatively short. There was a subsidence of the process without clinical evidence of the development of fluid in the pleural spaces.

The occurrence of jaundice in one patient presented a difficult diagnostic problem. It was impossible to decide whether there was an associated catarrhal jaundice or whether the pulmonary process was sufficient to lead to hepatitis. It was not thought that pulmonary infarction was a logical explanation in this case. Bezançon and Weil<sup>1</sup> reported a case in which there were pericarditis and pleuritis during the course of an acute attack of rheumatic fever in a patient with jaundice. Klemperer, Killian and Heyd<sup>2</sup> discuss this subject.

#### RHEUMATIC PLEURISY WITH EFFUSION

CASE 5.—An Irishman, aged 28, complained of pain in the joints for nine days before entry to the hospital. He had come to the United States five months previously. At the age of 13, and again, at the age of 19, he had been in a

1. Bezançon, F., and Weil, M. P.: *La maladie rhumatismale cardiopathie chronique à poussées successives sur le système séreux*, Ann. de méd. **19**:92 (Feb.) 1926.

2. Klemperer, P.; Killian, J. A., and Heyd, C. G.: *The Pathology of "Icterus Catarrhalis,"* Arch. Path. **2**:631 (Nov.) 1926.

transverse diameter of 14 cm.; the inner diameter of the chest was 28.3 cm. The mid-diastolic murmur had disappeared. Of several electrocardiographic examinations, one showed left ventricular predominance.

The leukocyte count on entry was 21,450, of which 89 per cent were polymorphonuclear leukocytes. The leukocyte count became normal after six weeks in the hospital; at the time of the patient's discharge it was 8,500, of which 55 per cent were polymorphonuclears. On entry, the red blood cells numbered 4,220,000 and the hemoglobin (Sahli) was 70 per cent. These decreased within six weeks to 3,600,000 and 62 per cent respectively. The urine showed a slight trace of albumin, occasional granular casts and red blood cells during the period of hyperpyrexia. There was no growth in four blood cultures. Sputum culture yielded *Streptococcus viridans* at the time of the patient's entry to the hospital.

This patient, who was seen in his third attack of rheumatic fever, when admitted showed polyarthritis, myocarditis, probable active endocarditis and pneumonitis. After admission, signs of fibrinous pericarditis and bilateral pleurisy, at first characterized by friction rub and then by bilateral effusions, appeared.

In all, ten patients were studied in whom the usual course was the development of pleural effusion following fibrinous pleurisy. Pleurisy in these patients lasted for weeks or months, in contrast to a period of days in the three patients in whom the lesion was only of a fibrinous nature.

Of the thirteen patients with rheumatic lesions of the pleura, the youngest was 15 years of age. Five patients were over 30 years.<sup>3</sup> The proportion of males to females was 10:3.

Coburn<sup>4</sup> has remarked on the rather high incidence of rheumatic fever in the immigrant classes, and thus it is to be noted that four of the six foreign-born patients had had no evidence of rheumatic fever prior to their arrival in this country. The other two patients had a recurrence of rheumatic fever soon after their arrival in America. Five other patients were the offspring of recent immigrants.

Cultures of venous blood were made in ten of the thirteen cases. In twenty-eight instances the cultures remained sterile. In one culture, *Streptococcus viridans* was obtained, but five additional blood cultures from this patient remained sterile.

#### HYDROTHORAX

CASE 14.—An American youth, 20 years of age was admitted to the hospital, complaining of painful, swollen joints. He had been treated in the hospital on four previous occasions for rheumatic fever; at the time of the first admission he had been 12 years of age. In the succeeding five years he was followed during several

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3. Patients who are admitted to the wards of the medical services of the Boston City Hospital are 12 years of age or older, which accounts for the absence of children in this series.

4. Coburn, A. F.: *The Factor of Infection in the Rheumatic State*, Baltimore, Williams and Wilkins Company, 1931.

# Synopsis of Fifteen Cases of Rheumatic Fever, Showing Pulmonary, Cardiac and Pleural Involvement

Rheumatic History				Cardiac Involvement				Pleural Involvement		
Case	Age and Sex	Poly-arthritis, Age of Patient	Tonsillitis	Pulmonary Involvement	Pericarditis	Endocarditis	Electrocardiographic Abnormalities			
1	15 F	9 and 12	None	Chorea, Age of Patient	Rarely	Pleural pain in left axilla twelve days before entry; recurrence of pain persisted for five days before entry; dulness, distant breath sounds and friction rub in left axilla; roentgenogram showed fine mottling throughout both pulmonary fields; symptoms and signs disappeared by end of first week	None	Mitral stenosis and regurgitation; aortic regurgitation (developed during period of observation)	QRS complex slurred all leads, T waves flat in all leads*	Fibrinous pleurisy, left
2	50 M	28	None	Frequently	On entry, dulness, decreased breath sounds and friction rub in left axilla; a few crepitant rales at both bases posteriorly; roentgenogram showed patchy density in both middle and lower pulmonary fields; bronchopneumonia; signs of infiltration appeared over left base to persist for a week	Fibrinous	Mitral regurgitation	.....	Fibrinous pleurisy, left	
3	41 F	38	None	.....	Signs of consolidation over right base, confirmed by roentgenogram, appeared one week after entry; friction rub at right base posteriorly one week after appearance of signs of consolidation; gradual disappearance of signs of consolidation during third week in hospital	Fibrinous ?	?	.....	Fibrinous pleurisy, right (jaundice—icteric index 75 on entry; gradual decrease)	
4	33 M	None	None	Frequently	Severe pleural pain in right lower part of chest, subsiding for four days; signs of fluid with overlying friction rub at right base; roentgenogram showed fluid in lower third of right side of chest; following pleurocentesis, frank signs of consolidation persisted for five weeks	None	?	Partial heart block (PR interval, 0.2 to 0.28 sec.); T <sub>3</sub> diphasic or inverted*	Pleural effusion, right	

5	23 M	13 and 19	None	Occasionally	Persistent cough for six days before entry; on entry, a few coarse râles at the left base, dulness, bronchovesicular breath sounds at the right base posteriorly and at the apex anteriorly; roentgenogram showed patchy density in both pulmonary fields, more marked on the right; signs unchanged until the right rib ten days later in the left axilla and effusion at the right base; fluid removed; signs of patchy consolidation and a small amount of fluid bilaterally persisted	Fibrinous	Mitral stenosis and regurgitation	Left ventricular pre-dominance	Pleural effusion, bilateral
6	21 M	9	None	Rarely	On entry, a few fine râles throughout the chest; roentgenogram showed patchy lobular density at both bases; two weeks later, fluid at the right base; signs of consolidation at the right base followed and persisted for two weeks	Effusion (small)	Mitral stenosis and regurgitation	T <sub>1</sub> inverted*	Pleural effusion, right
7	27 M	13	None	Rarely	On entry, examination of the chest gave negative findings; four days later, consolidation of lower half of both lungs, followed by fluid at both bases; pleurocentesis and finally resorption after one month	Fibrinous	Mitral regurgitation	Deep Q <sub>2</sub> , T waves inverted*	Pleural effusion, bilateral
8	16 M	11, 13, 14 and 15	None	.....	Pain in right side of chest, subsiding for two weeks; on entry, fluid at the right base; slight dullness, exaggerated breath sounds and crepitant râles at the right apex; pleurocentesis; disappearance of signs after five days	None	Mitral stenosis and regurgitation	Normal	Pleural effusion, right
9	1 M	6 and 13	None	.....	On entry, examination of the chest gave negative findings; roentgenogram showed slight cloudiness at left apex; two weeks later, fluid at the left base; pleurocentesis; consolidation in the left lower part of chest for two weeks	None	Aortic regurgitation	Paroxysmal tachycardia (auricular); partial heart block (PR interval up to 0.44 sec.); left bundle branch block; left ventricular preponderance; deep Q <sub>2</sub> , QRs cleared all leads; T waves all normal	Pleural effusion, right



# Synopsis of Fifteen Cases of Rheumatic Fever, showing Pulmonary, Cardiac and Pleural Involvement—Continued

Rheumatic History			Cardiac Involvement				Pleural Involvement
Case	Poly-arthritis, Age of patient	Chorea, Age of Patient	Tonsillitis	Pulmonary Involvement	Pericarditis	Endocarditis	
10	37 M	None	Occasionally	Bilateral pleural pain two days before entry; fluid at both bases overlying friction rubs in axillae; friction rub absent three days later, fluid persisted for five weeks	Fibrinous, followed by effusion (small)	Mitral regurgitation	Pleural effusion, bilateral
11	28 M	None	Occasionally	On entry, fluid at both bases, confirmed by roentgenogram; signs at right base absent after two weeks; after two weeks, signs of consolidation at right base reappeared to persist for another two weeks	Fibrinous, followed by effusion (moderately large)	Aortic regurgitation	Pleural effusion, bilateral
12	15 F	None	Rarely	On entry, dulness, exaggerated breath sounds, a few râles over left apex and in left axilla; a small amount of fluid at both bases; all signs disappeared after three weeks	Effusion (moderate)	Mitral stenosis and regurgitation	Pleural effusion, bilateral
13	35 M	None	Frequently	On entry, dulness and crepitant râles at angle of right scapula; a small amount of fluid at right base, disappeared after six days; three days later, a large amount of fluid at left base, resorbed after ten days	None	Mitral regurgitation	Pleural effusion, bilateral
14	20 M	9, 12 and 17	Frequently	On entry, dulness, increased voice sounds and medium moist râles at angle of left scapula; roentgenogram showed cloudy pulmonary fields (stasis); rapid accumulation of fluid at both bases, with other signs of myocardial failure	Fibrinous (fibrous)	Mitral stenosis and regurgitation; aortic regurgitation	Pleural effusion, bilateral; myocardial failure (died, autopsy)
15	21 F	15 and 17	Frequently	On entry, scattered moist râles at both bases; flatness at the extreme bases; gradual disappearance of signs within a few days	None	Mitral stenosis and regurgitation	Pleural effusion, bilateral; myocardial failure

\* Digitalis not being given at the time of record.

and obvious myocardial damage. The course was that of a severe rheumatic infection with rapid myocardial failure leading to death. Autopsy revealed peripheral edema, bilateral hydrothorax, fibrous and fibrinous pericarditis, cardiac hypertrophy and active aortic and mitral endocarditis.

During the course of an exacerbation of rheumatic fever, pleural effusion may occur which is secondary to myocardial failure. With an acute exacerbation of the disease, the margin of reserve of the myocardial efficiency may be sufficiently impaired, either as a result of the myocardial involvement itself or because of the added burden of a more or less severe febrile disease, with or without the mechanical handicap due to valvular lesions, to lead to definite evidence of cardiac decompensation. Pleural effusion under these circumstances must not be confused with an effusion which is the direct result of rheumatic lesions of the pleural and underlying structures.

The more important clinical features of the cases studied are summarized in the table.

#### PULMONARY LESIONS

In reviewing the records of the thirteen patients who had pleural lesions as a feature of rheumatic fever, one is impressed by the frequency with which physical signs and roentgenologic evidence of involvement of the lung itself were observed. In each of the three cases of fibrinous pleurisy there was clinical evidence of pathologic changes in the lungs. Of the ten patients showing rheumatic pleurisy with effusion, five showed signs in the lung elsewhere than where pleural lesions were detected. In four patients, the signs of consolidation in the underlying lung were found after removal or absorption of the fluid. In two patients, pulmonary lesions were diagnosed prior to the appearance of signs pointing to pleural involvement. It seems significant that a pneumonic process was present in the patients in whom pleural lesions were encountered.

#### CARDIAC INVOLVEMENT

Endocardial lesions were diagnosed in eleven of the thirteen cases of rheumatic pleurisy. In nine cases, the process was confined to the mitral valve; two patients had aortic regurgitation, and in one case, which showed signs of mitral disease on entry, aortic regurgitation developed.

An associated pericarditis was diagnosed in eight of the thirteen cases; in four, the process was a fibrinous one; in the other four were signs of pericardial effusion subsequent to a fibrinous process which, however, never gave sufficient trouble to require removal.

There was no reason to suspect myocardial failure in the thirteen cases of rheumatic pleurisy. The clinical picture and the course of the illness in those patients who had effusions differed materially from

those of the two patients in whom there were bilateral effusions obviously resulting from myocardial failure.

The electrocardiogram gave abnormal deflections in nine of the ten cases studied. Paroxysmal auricular tachycardia, partial heart block and left bundle branch block were noted in a series of studies on one patient. The PR interval was prolonged beyond the normal limits in three other patients. Sino-auricular tachycardia occurred at times in three patients.

#### ONSET OF PLEURAL AND PULMONARY LESIONS

Polyarthrititis preceded the symptoms referable to the thorax in eleven of the thirteen cases. In one instance, a sore throat was followed in two weeks by symptoms pointing to pleural and pulmonary lesions; joint symptoms did not appear until two weeks after the onset of the thoracic symptoms. In the other case, joint symptoms followed the onset of pericardial and pleural symptoms within six days.

In eight of the thirteen cases there was clinical evidence of acute pericarditis. The pleura was involved bilaterally in six cases. The right side alone was the site of a pathologic process in four instances, the left side alone in three instances. The onset of the pericardial lesion apparently preceded the pleural and pulmonary involvement in four of the eight cases. In two of these four cases there was at no time evidence of any active process localized in the left pleura, the pleural lesion being on the right side only. Involvement of the right side alone or primarily, followed by lesions in the left side and in the pericardium, occurred in six cases. The left lung and pleura were either the primary or the single site of an active process in two cases.

In this series of cases there seems to be a close association of pleural and pericardial lesions. However, there is little evidence that the pleural lesions were secondary to, or the result of, an extension from pericardial lesions. Howard<sup>5</sup> was of the opinion that the process in the pleura was probably an extension from the pericardium; similar conclusions have been drawn by subsequent observers. It would seem more probable that the pleural lesions are evidences of a more or less independent manifestation of the disease. The recognition of widespread vascular lesions in rheumatic fever has removed the necessity of relying on the explanation that pleural infection is an extension from the pericardium. The pleural lesions encountered in rheumatic fever may be due either to an extension from underlying pulmonary lesions or to processes simultaneously involving the pleural and subpleural layers, the cortico-pleuritis of Bezançon and Weil.<sup>6</sup>

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5. Howard, R. P.: Rheumatism, in a System of Practical Medicine, by American Authors, edited by William Pepper, Philadelphia, Lea Bros. & Co., 1885, vol. 2, p. 19.

6. Bezançon, F., and Weil, M. P.: La cortico-pleurite rhumatismale, *Ann. de méd.* 19:184 (Feb.) 1926.

## PREVIOUS RHEUMATIC EPISODES

Of thirteen patients, three were seen in their first definite attack of rheumatic fever. The remaining ten patients had had from one to four previous attacks. In no patient was there any previous pulmonary and pleural involvement of a similar nature.

Colds in the head and tonsillitis were of common occurrence in five cases. In ten of the thirteen cases, the illness was preceded by an acute infection of the nasopharynx. In two other cases, examination of the pharynx and the tonsils revealed evidence of an acute infectious process.

## CHARACTERISTICS OF PLEURAL FLUID

Seven specimens of pleural fluid from six patients were examined. These specimens were similar in most respects. Fluid was removed at intervals of two to fourteen days after the onset of symptoms and signs. Removal of the fluid was thought to be advisable from a therapeutic standpoint in but three instances. The most striking characteristics of the fluid were the hemorrhagic appearance and the readiness with which clot formation took place. The fluid from two patients was grossly bloody, while that from three other patients contained a sufficient number of erythrocytes to give it a pinkish-yellow color. Within ten or fifteen minutes after the withdrawal, the fluid in each of the seven cases formed a coagulum which enmeshed the cellular elements, leaving a clear, straw-colored fluid. This characteristic, repeatedly noted by numerous observers, has been ascribed to the high fibrin content. The cytologic studies were subject to variations too great to permit comparison. The leukocytes were not numerous, the counts varying between 600 and 3,750 per cubic millimeter.

Cultures of pleural fluid in each instance showed no growth. Guinea-pigs inoculated with specimens of fluid from three patients failed to show lesions characteristic of tuberculosis.

## CLINICAL COURSE

In eleven of the thirteen cases, the illness began as polyarthritis; the onset of symptoms pointing to inclusion of the pericardium, lungs or pleura appeared during the second week of the illness except in three instances, in which the intervening period was but a few days. The onset of dyspnea, orthopnea, occasional mild cyanosis of the mucous membranes and pleural pain was sudden. Even in the cases in which pericardial lesions were absent or could be considered as negligible, the certainty of pulmonary lesions made the interpretation of the symptoms confusing. Dyspnea and orthopnea seemed out of all proportion to the extent of the process demonstrable. This disproportion between the severity of respiratory symptoms and the extent of pulmonary lesions has been commented on by Naish.<sup>7</sup> The severity of the dyspnea,

7. Naish, A. E.: The Rheumatic Lung, *Lancet* 2:10 (July 7) 1928.

orthopnea and cyanosis was subject to marked alteration almost from hour to hour, without demonstrable changes in the physical findings.

The sputum was noted as being small in amount, tenacious and occasionally mucopurulent. In only one patient was the sputum grossly bloody, and this patient was subject to epistaxes during the period in which bloody sputum was observed.

The fever was of a continuous nature, with occasional slight remissions in twelve of the thirteen cases; in the other case, the temperature was irregularly intermittent. The temperature by mouth was 103 F. or higher at times, in seven cases. In no instance during the activity of the thoracic lesions did the temperature remain below 101 F. The maintenance of the temperature above 100 F. was subject to great variability; in one patient it remained above this point for twenty-nine days. The temperature approached a normal level with the subsidence of the thoracic lesions.

#### THERAPY WITH SALICYLATES

Sodium salicylate in doses ranging from 45 to 150 grains (2.9 to 9.7 Gm.) per day was administered with a similar amount of sodium bicarbonate. In no instance could it be said that the medication had any striking effect on the pleural or pulmonary lesions. This is in accord with the observations of Caussade and Tardieu<sup>8</sup> and of Grenet.<sup>9</sup> In one case therapy with salicylates was not instituted until after the subsidence of the pleural lesions—a period of approximately two weeks. No salicylates were given to another patient while she was in the hospital, and after ten days her temperature gradually fell, with disappearance of signs of pleural and pericardial lesions. The course of the processes in the lungs and pleura seemed not to differ essentially in those cases in which therapy with salicylates was withheld. Consistently the joint symptoms either disappeared or were lessened in severity following the institution of therapy with salicylates. However, with the onset of symptoms pointing to involvement of the lung and pleura there was a recurrence of the joint symptoms and signs, usually of a mild nature. The articular manifestations persisted, in spite of the therapy with salicylates, until effervescence of the pleuropulmonary lesions.

#### SUMMARY

Fifteen cases of rheumatic fever with pleural lesions were studied. Thirteen patients had rheumatic pleurisy; three, fibrinous pleurisy, and ten, pleurisy with effusion. Two patients had bilateral hydrothorax owing to myocardial failure during the acute stages of rheumatic fever.

8. Caussade, G., and Tardieu, A.: *Classification clinique et thérapeutique des pneumopathies rhumatismales*, Paris méd. **2**:157 (Aug. 23) 1930.

9. Grenet, H.: *Les formes cliniques de la maladie rhumatismale (rhumatisme articulaire aigu et formes extra-articulaires)*, Monde méd., Paris **40**:809 .) 1930.

Involvement of the pleura was characterized by suddenness of onset and by dyspnea, orthopnea, mild cyanosis, pain (depending on the nature of the pleural lesion) and a febrile response varying in severity and duration.

Evidence pointed to concurrent pulmonary lesions in the patients who had true rheumatic pleurisy.

The pleural lesions were found to be independent of pericarditis and were related to underlying pulmonary processes.

The hemorrhagic nature and the readiness with which clot formation took place characterized the fluid of rheumatic pleurisy.

Polyarthrititis was preceded by involvement of the pleura and lung in two instances.

Salicylates did not alter the course of the pleural and pulmonary lesions and, indeed, failed to relieve completely the articular symptoms in the presence of an extension of the rheumatic process to the pleura and lung.

## Book Reviews

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**Physiological Effects of Radiant Energy.** By Henry Laurens. Price, \$6. Pp. 609. New York: The Chemical Catalog Company, Inc., 1933.

There has been so much discussion in the medical literature and quasimedical publications, often biased and without scientific foundation, that an authoritative book dealing with the effects of radiant energy on the body is to be welcomed. The vendor of the apparatus for radiant energy may insist, and even the user of various types of lamps may persuade himself, that there is a tremendous amount of virtue in artificial sunlight. There can be no question but that such is the truth; on the other hand, however, carbon arc lamps, ultraviolet lamps, quartz lamps or other types of lamps giving radiant energy are not the cure-alls that many believe them to be. It is therefore important that there be such a book as this which contains within it an unbiased, well balanced, scientific compilation of the use of radiant energy by one who has done a large amount of experimental work and who has made definite contributions to the subject.

Following the introductory sections there is a long chapter on the physics of radiant energy. Then follow chapters on the effects of radiant energy on the skin, wounds, the circulatory system, the blood, the metabolism, the body temperature, tuberculosis, bacteria and micro-organisms, toxins, antitoxins and so on. A bibliography of sixteen pages follows, succeeded by a complete index of authors and an equally complete index of subjects. The section on the effects of radiant energy on metabolism is most complete. Five chapters are devoted to this particular phase of radiant energy; naturally a not inconsiderable section has to do with the prevention and cure of rickets and the relationship of the ultraviolet rays to vitamin D.

This brief summary indicates the type of volume which Laurens has prepared so successfully. In the preface he states that he has compiled "a source book to which interested persons might resort to obtain information on the main work that has been done in this or that special field." With this purpose in mind the author naturally has not drawn conclusions. A criticism, which may or may not be valid, is that it does seem that the value of the book would be enhanced if conclusive statements were made by the author as one more fully qualified to elucidate contentious points than is the reader.

**L'aérophagie et son traitement.** By Félix Ramond, Physician to the Hôpital St.-Antoine, Paris, and Dimitresco-Popovici, Physician to the Hôpital Regina-Elisabeta, Bucharest. With the Collaboration of H. Dany. Paper. Price, 17 francs. Pp. 132, with 10 illustrations. Paris: Masson & Cie, 1933.

**Les constipations.** By M. Chiray, Physician to the Hôpital Bichat, Paris, and R. Stieffel, Consulting Physician at Plombières. With a historical note by Jean Vinchon, former Chief of Clinical Psychiatry, the Faculty of Medicine, Paris. Paper. Price, 20 francs. Pp. 157. Paris: Masson & Cie, 1933.

In 1923, Masson & Cie began to publish a series of short monographs under the name "Collection médecine et chirurgie pratiques." These monographs evidently have won a considerable degree of popularity, judged by their rate of growth, for up to the beginning of 1933 fifty-seven had appeared. In 1933 the two monographs with the titles mentioned have been printed, and one on the treatment of diabetes by Marcel Labbé is on the press.

Each monograph is short, inexpensive and, judging by the two latest samples, well printed on good paper. The group as a whole covers a wide range of subjects. A few of the volumes have been reviewed in *The Journal of the American*

*Medical Association.* They are well spoken of and appear to fulfil the purposes for which they were published, namely, to offer physicians a practical collection of booklets on subjects dealing with current medical and surgical knowledge. They are inexpensive, but are readable and easy to carry.

The monographs on aerophagy and constipation are merely additions to the series. The swallowing of air and its treatment are illustrated with roentgenographic charts and are disposed of in a sufficiently interesting fashion. There is an admirable historical account of constipation. The organic causes of chronic constipation are well discussed, so that the functional aspects of this habit are not unduly emphasized. On the whole, both monographs help to supplement the series and to make the collection of increasing interest to practitioners.

**Clinical Aspects of the Electrocardiogram.** By Harold E. B. Pardee, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College. Third edition. Price, \$5.50. Pp. 295, with 74 illustrations. New York: Paul B. Hoeber, Inc., 1933.

The first edition of this book was published in 1924. It cost \$4 and contained 222 pages with 56 illustrations. It was reviewed in the *ARCHIVES* (34:737 [Nov.] 1924) and in *The Journal of the American Medical Association* (83:1359 [Oct. 25] 1924). Both reviews spoke well of it, complimenting the author on his clarity of style and manner of presentation and predicting that this work would prove of practical value not only for reference but also in the clinic.

A second edition was published in 1928. By that time the volume had grown in size and was more expensive. It cost \$5.50 and contained 242 pages with 60 illustrations. The second edition also was reviewed in the *ARCHIVES* (43:891 [June] 1929) and in *The Journal of the American Medical Association* (91:1181 [July 14] 1928). Both reviews again spoke cordially of the book and of the comprehensive manner in which the material had been put together. The second edition proved even more popular than the first and appeared to fill a considerable demand, as a reprinting was necessary in 1930.

The third edition has now appeared, a little longer in text and more profusely illustrated than its forbears, but otherwise conforming closely to their standards and form. There is little more to be said.

Dr. Pardee has brought his material up to date, changing or adding bits here and there in order to maintain his book at the level suggested by its title. In view of the enthusiastic way in which the preceding editions have been received, there is every reason for anticipating an equal success for the third. It is the kind of book that libraries, students, cardiologists and general practitioners will wish to own. It is recommended highly.

**Methods and Problems of Medical Education.** Twenty-First Series. Nursing Education and Schools of Nursing. Pp. 226. New York: Rockefeller Foundation, 1932.

This volume, the last of a series of twenty-one devoted to medical education, is on nursing education and schools of nursing. The study includes some of the outstanding nursing schools of the world. In the United States the schools that are used for examples of the advancement in nursing education are frequently connected with universities and in all respects are on the same level as the other departments of the university. This indicates that requirements for entrance to schools of nursing are more stringent than formerly and emphasizes the necessity for young women with good educational and cultural backgrounds. The ratio of theory to practice is another important factor. The advanced schools are constantly experimenting on the amount of theory that should be given with clinical experience. One of the accepted ratios is that seven hours of practical experience for fifteen weeks count as one lecture hour. Fifteen per cent of the course is devoted to theory. This is interesting, as at present there is considerable comment about the amount of theory a nurse should have.



Nursing schools in foreign countries present much the same problems as those in the United States. However, in many of the countries the most outstanding schools are based on the American plan of nursing education. Since standards of nursing education are changing along with standards of education in other fields, there is a question as to whether the present system of training the nurse is the wisest. Unquestionably, as more is required and expected of a nurse today than formerly, one who wishes to qualify as a nurse must recognize the necessity for intensive study and a conscientious desire to give service.

**Der Weg zur rationellen Therapie.** Edited by Prof. Dr. A. Fraenkel, Heidelberg. Price, 10.80 marks. Pp. 183. Leipzig: Georg Thieme, 1933.

This book consists of reports of lectures given at Heidelberg in August, 1932, which correspond to what in America would be called a postgraduate course, the purpose of which is to discuss "the exact use of specific therapeutic agents on the basis of their pharmacologic action." Mercury, digitalis, thyroxine, arsphenamine, the vitamins and antianemic liver preparations receive consideration by such authorities as Straub, Sachs, György, Gänzlen and others. The summaries bring the subjects up to date in an adequate manner, and the bibliographies attached to some of the articles are especially useful.

**Radiologic Maxims.** By Harold Swanberg. Price, \$1.50. Pp. 127. Quincy, Ill.: Radiological Review Publishing Company, 1932.

This small book represents a collection of certain radiologic maxims which have appeared in the last six years in the *Radiological Review* and the *Chicago Medical Recorder*. There are additional quotations which have to do with various radiologic subjects. Necessarily the maxims are dogmatic, succinct and in some instances questionable. Apparently these maxims are written for the radiologist primarily, because the claims that they make for the x-rays in diagnosis and in therapy are a bit too comprehensive for any one but a rabid enthusiast to swallow whole.

## ULTIMATE RESULTS OF THORACOPLASTIC OPERATIONS IN PULMONARY TUBERCULOSIS

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In evaluating the ultimate results attained in the surgical treatment of pulmonary tuberculosis, the vast majority of authors have based their opinions on statistics showing the proportion of patients who have recovered, improved, remained unchanged or died. While the number of cases reported statistically has, on the whole, been ample, it appears that most authoritative investigators have not felt completely convinced that their statistics were entirely conclusive regarding the value of this mode of treatment. This is clearly seen from the writings of Sauerbruch, John Alexander and others. Few authors have given adequate details of a long series of cases, describing the clinical history of each patient before and after the operative procedure.

As the statistical results attained by this form of treatment at the Montefiore Hospital—and what is more important our impression as practicing physicians regarding the benefit to the individual patient—differ drastically from those reported from other institutions, we have decided to publish our cases in detail. Each case is treated as a unit—each patient as an individual and not merely as one in a series. The salient points in the history of the patient before operation are given, and the course of the disease after operation is described. We believe that only thus can the clinician form an opinion as to the ultimate results attained by the various thoracoplastic operations in vogue during recent years.

Our clinical material is of unusual diversity for it comes from two institutions, the country sanatorium where patients with early or hopeful cases are admitted and the hospital in the city where those with advanced and progressive cases are cared for. All surgical operations are performed in the hospital, and the patients requiring treatment after operation are sent to the sanatorium for convalescence or further rest

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From the Tuberculosis Division of the Montefiore Hospital and its sanatorium at Bedford Hills, N. Y.

treatment under our observation. Moreover, the social service department follows each patient after discharge, urging recalcitrant ones to attend the outdoor clinic. All this enables the staff to follow each case throughout its clinical course. Only rarely have we had to obtain information as to the condition of the patient by mail.

It will be noted from the histories of the cases here reported that nearly all of the patients had been given therapeutic pneumothorax, which may or may not have been effective in ameliorating the symptoms, but sooner or later it had to be abandoned because of pleural effusions, obliterative pleuritis and similar conditions. In others, the pneumothorax treatment was effective in staying the course of the disease; the patient recovered and returned to industrial activity, but sooner or later a relapse occurred. Attempts at reinduction of pneumothorax proved futile because of pleural adhesions. Hence, thoracoplasty was done with a view to collapsing the affected lung.

Of course, the ideal patient for thoracoplasty is one with a unilateral lesion tending to sclerosis, with mild or but slight symptoms of progressive disease. Patients with bronchopneumonic lesions, with the disease pursuing a dynamic clinical course, with high fever and other symptoms, almost invariably respond adversely to the operation. In other words, patients suitable for thoracoplasty in any of its forms usually get along fairly well and are not in imminent danger, even though febrile exacerbations disable them for days or weeks at irregular intervals. But they recuperate to the degree that they feel quite comfortable. During the periods of recession of dynamic activity many are not fit for remunerative callings because of the cough, more or less copious expectoration, perhaps some subfebrile temperature, fatigability and liability to exacerbations coming with, or without, any obvious cause. These patients are apt to beg for anything that may relieve them; they do not want to remain invalids or inmates of institutions for life.

#### ACTIVE PARENCHYMATOUS CASES

The following are some cases of this type:

CASE 1.—A. H., a woman, aged 28, was admitted to the hospital on May 6, 1924, with a history of an attack of pleurisy five weeks previously. Examination showed extensive bronchopneumonic infiltration throughout the left lung. The course was active and febrile. She was transferred to the country sanatorium, where therapeutic pneumothorax was induced and was continued for eight months with, on the whole, unsatisfactory results. Despite the frequent acute febrile attacks, which the pneumothorax failed to prevent, and signs of a sclerotic lesion in the apex of the right lung, we considered her a good operative risk. The operation was done in two stages, on Nov. 29 and Dec. 22, 1926. In the early months of the following year, 1927, as long as the patient remained in the hospital she continued afebrile; her general condition was good, but the physical and roentgen signs still indicated cavitation in the collapsed lung. In May, 1927, she was

again transferred to the sanatorium, where her general condition continued good, but the signs of cavitation persisted. In December, 1928, she was discharged. Since then she has remained at home and attends the outpatient clinic regularly.

She attends to her household duties, but because of fatigability and mild febrile exacerbations, which have of late been rather short-lived, she has not engaged in any gainful occupation. It appears to us that if the symptoms, physical findings and roentgen signs are taken into consideration, she could be considered by any clinician a suitable subject for thoracoplasty.

CASE 2.—P. B., a man, aged 28, a salesman, was admitted to the hospital on June 10, 1926, with a history of recurrent hemoptysis for seven years, fever, cough and expectoration. For copious and threatening hemorrhages, a hemostatic pneumothorax was attempted, but it failed to stay the bleeding. On examination, an extensive right-sided lesion with cavitation of the upper lobe and a markedly thickened pleura were disclosed. Trachea, heart and mediastinal contents were displaced into the right side of the chest. A two-stage operation was performed on June 12 and July 9, 1926. Within a few months after the operation, the patient's cough and expectoration lessened, and he felt somewhat improved. He was discharged from the hospital in August, 1926. On follow-up, a report from his doctor in December, 1928, revealed that he was not symptom-free. On Aug. 7, 1929, the report from the same doctor was to the effect that the patient was working as the village clerk for a few hours daily. The last report on June 7, 1932, is to the effect that he is still engaged as the village clerk. However, he is not free from symptoms of tuberculosis; he still coughs, expectorates and cannot work regularly, being incapacitated now and then by symptoms of activity.

In this case the patient has survived for six years following thoracoplasty and for thirteen years since the onset of his tuberculous disease. He has not been fit to reengage in his occupation because he is still suffering from the symptoms of chronic phthisis and is unfit for work requiring regularity and persistence.

CASE 3.—A. G., a woman, aged 40, was admitted to the hospital on Jan. 3, 1929, with a history of cough and expectoration for two years. A year after the onset, she became actively febrile and suffered from hemoptysis. Six pneumothorax insufflations were given in 1928 without benefit. Examination at the time of admission revealed an extensive fibrocaseous and cavernous lesion of the left lung showing strong tendencies to fibrosis. During her stay in the hospital she was afebrile and ambulant, and gained 20 pounds (9 Kg.); she was discharged on Feb. 4, 1930. After being home for a short time, she was readmitted to the hospital because of a subacute exacerbation, and on routine treatment she again improved and gained 30 pounds (13.6 Kg.) in weight. She was again discharged, but at home symptoms of activity recurred. She was readmitted to the hospital on May 22, 1931, and one week later phrenicectomy and thoracoplasty were performed without any immediate untoward effects, except that pain at the site of the operation persisted. Six months after the operation an examination revealed physical and roentgen signs of an uncollapsed cavity in the upper lobe of the left lung. However, her general condition was considered excellent for the time being, and she was discharged on Feb. 6, 1932.

Our clinical opinion is in the direction of considering the patient's present state as one of remission in activity, such as had repeatedly

occurred before the surgical intervention. She is still sick with chronic pulmonary tuberculosis, coughs and expectorates, and is unfit to engage in any gainful occupation requiring steadiness in activity. She is dyspneic on slight exertion and tires easily. She had these same symptoms for three years before the operation was performed.

CASE 4.—F. B., a woman, aged 25, was admitted to the hospital on Jan. 29, 1925, with a history of having tuberculosis for five years which followed a sluggish course. Examination disclosed a unilateral lesion confined to the right lung with extensive cavitation in the upper lobe and evidence of marked fibrosis. The temperature ranged between 100 and 103 F., and the patient was losing weight. Thoracoplasty, first stage, was performed on April 18; the second stage, on May 6, and phrenicectomy, on July 15. Seven months later, the following note was entered on the chart: "Numerous large consonating râles and bubbles in upper half of the right chest, indicative of cavitation, clearly seen on the roentgenogram, and marked dextrocardia." The patient's general condition was satisfactory; no toxic symptoms were present, and she had gained in weight. She was then transferred to the sanatorium, where she remained for twenty months. From there she went to a private sanatorium, and has continued to be under medical care, as she had been prior to the operations performed seven and one-half years ago. She is still "taking the cure."

CASE 5.—R. H., a woman, aged 42, was first seen on April 10, 1923, with a history of a bronchopneumonic onset. At the sanatorium a therapeutic pneumothorax was induced with beneficial results, and she was discharged improved on April 17, 1925. She remained home in fairly good health for three years and was admitted to Montefiore Hospital on May 30, 1927, because of symptoms of reactivation of the disease. We then found symptoms and signs of cavitory phthisis in the right lung, a thickened pleura and dextrocardia. In fact, the signs indicated changes not unlike those obtained after an average successful thoracoplasty. Because of persistence of constitutional symptoms, surgical intervention was decided on.

The first stage of thoracoplasty was performed on July 12; it was followed by postoperative shock, lasting twenty-four hours. The second stage was done on July 19. For the next two years the patient remained in the hospital or the sanatorium, alternately, continuing "the cure." She was discharged on May 26, 1929, feeling fairly well, and went home and attempted to do her housework. A sudden, copious hemorrhage, followed by cough, weakness and moderate fever, again disabled her. During the next four months, she lost 35 pounds (15.9 Kg.) in weight. Examination in December, 1930, revealed signs of extensive infiltration and a large cavity in the right upper lobe which the surgical collapse failed to obliterate. There was a dense pleuritis over the lower half of the right lung, marked dextrocardia and a fibroid process in the left upper lobe.

On Sept. 20, 1931, she again had a profuse hemorrhage. She continued to bleed for eight days. It appears that her general condition hardly differed from what it had been previous to the operative intervention. A noteworthy phenomenon is that this patient who never bled prior to the operation has since then sustained three copious pulmonary hemorrhages. She is bedridden, dyspneic and unfit for any worthwhile activity. She was discharged on Nov. 10, 1932. She is still under treatment for pulmonary tuberculosis.

CASE 6.—Y. W., a woman, aged 25, was admitted to the hospital in March, 1927, with a history of an acute onset in January, 1927, followed by hemoptysis

in March, 1927. Pneumothorax was induced, collapsing the left lung. The treatment was effective; the patient felt well and was afebrile, but insufflations had to be discontinued within eight months because of pleural adhesions. She was discharged in March, 1929, the process being considered quiescent. At home she suffered exacerbations of symptoms, which necessitated readmission on Sept. 14, 1929. She remained until June 11, 1930, when she was transferred to another hospital. At the time of the present readmission to Montefiore Hospital on Oct. 9, 1930, she showed signs of extensive fibrocaseous tuberculosis throughout the entire left lung, with a large cavity in the upper lobe. Constitutional symptoms, cough, expectoration and moderate fever were pronounced. Marked fibrosis of the lesion with a narrowing of the entire left hemithorax and sinistocardia were salient features of the case. The right lung did not show any physical signs of active tuberculosis, but a roentgenogram revealed an old calcific area.

Phrenicectomy was performed with no apparent effect on the cough or expectoration. Thoracoplasty was performed in three stages on Jan. 1, March 9 and April 15, 1931, and again no immediate salutary effects resulted. The patient complained of tightness in the left side of her chest, dyspnea and marked difficulty in raising sputum. One year after the operation, a marked collapse of the left hemithorax was evident, but the cavity in the upper lobe was clearly obvious. Periods of fever of 102 F., lasting several days or weeks, interspersed by afebrile periods have been salient features of the case.

Evidently here the operative intervention has not in any way favorably altered the course of the disease; the chronic, slowly progressive course with exacerbations and remissions remained as before the operation. After the lapse of another year, no favorable change is evident, but the patient has annoying tachycardia, palpitation and cyanosis. She is bedridden.

CASE 7.—P. W., a woman, aged 22, was seen on April 1, 1924, with a history of an insidious onset eight months previously. The last four months the fever was high and continuous. Artificial pneumothorax was induced on the right side on April 24. The results being unsatisfactory and fever continuing high, she was transferred to the hospital on May 27. Here it was noted that the failure of the pneumothorax therapy was evidently due to inadequate collapse of the lung; a caseous lesion in the lower lobe could not be collapsed because this portion of the lung was anchored by adhesions, while the cavity in the upper lobe had also remained open. The left lung was apparently free from active disease. Surgical intervention was decided on. Phrenicectomy was first performed on June 24, and one month later, July 25, the first stage of thoracoplasty was started. After the second operation, performed on October 5, the patient reacted with rather severe shock. The pulse rose to the rate of 140 and became very weak. Active stimulation was required. Two months subsequent to the second stage, the patient appeared improved; the cough and expectoration lessened. Six months postoperatively, her general condition was considered encouraging. She was ambulant, afebrile and gained 26 pounds (11.8 Kg.) in weight. She was transferred to the sanatorium, where she remained for a year and was finally discharged with the process "arrested" on April 16, 1927. One year later she suffered from a relapse of the symptoms indicating activity of the disease. She was readmitted to the sanatorium in October, 1928, and remained there until January, 1930, at which time the pulmonary lesion was found quiescent and the sputum negative. She was

considered fit to work six hours a day as a nurse's attendant. In December, 1931, she suffered another relapse and was readmitted to the sanatorium as a patient. Physical and roentgen evidence of a bronchopneumonic lesion in the contralateral part of the lung was found, and the sputum again became positive for tubercle bacilli. The patient improved on routine therapy, finally becoming symptom-free. Physical and roentgen examination revealed that the bronchopneumonic process in the left lung had *undergone almost complete involution*. It is noteworthy that the right lung, collapsed by the thoracoplastic operation, was apparently unaffected during this episode.

In retrospect, we find in this a case of intensely chronic pulmonary tuberculosis with the commonly observed cyclic course: exacerbations interspersed with remissions. The patient is still tuberculous clinically. That the thoracoplasty contributed to her comfort or prolonged her life is open to question.

CASE 8.—C. G., a woman, aged 25, was admitted to the hospital on March 5, 1929, with a history of bronchopneumonic onset of nine weeks' duration. On admission we found an extensive bronchopneumonic process in the left upper lobe with moderate-sized cavity formation below the clavicle. Pneumothorax was attempted, but no effective collapse could be obtained because of pleural adhesions. Under expectant treatment the patient felt well, became afebrile and gained 40 pounds (18.1 Kg.) in weight. Six months later, it was noted that in spite of the gain in weight she felt worse subjectively. She coughed excessively, had a subfebrile temperature and was short-winded. Physical and roentgen examination revealed an extensive fibrocaceous lesion involving the entire left lung and the cavity enlarged involving the entire upper lobe. Thoracoplasty was performed in two stages, on Nov. 12, and Dec. 3, 1930. The postoperative course was stormy after each stage. Cough and expectoration were reduced for a few months, but again increased to the original intensity. On Jan. 28, 1931, a supplementary phrenicectomy was done. Roentgen examination showed that the cavity was not markedly reduced in size, despite thoracoplasty and phrenicectomy.

In April, 1932, she still had tachycardia and dyspnea; cough and expectoration persisted, and the sputum was still positive for tubercle bacilli. Physical and roentgen signs still showed unequivocal evidence of extensive tuberculosis throughout the entire left lung with multiple cavities of the upper lobe. In the vocabulary of the sanatorium the process might still be considered "quiescent," but by no means "arrested."

CASE 9.—W. G., a man, aged 28, was admitted to the sanatorium in July, 1932. The onset of his condition in March, 1926, was bronchopneumonic in type with hemoptysis. He was at a sanatorium for one and one half years, where pneumothorax was induced and continued during the entire stay. He was discharged with no symptoms of active disease and negative sputum. He remained well for two years, when a relapse occurred. Thoracoplasty was performed in December, 1931, and in May, 1932. The delay between the two stages was caused by a severe infection of the wound complicating the first operation which healed only after a lapse of three months. However, the cavities have remained open in the upper lobe. The patient is afebrile, but suffers from marked asthenia. The sputum is still positive, and he must continue "the cure" at the sanatorium.

CASE 10.—B. R., a man, aged 26, had cough, fever and hemoptysis in 1927. He lived in a tuberculosis health resort until 1931. He received pneumothorax therapy

on the right side from June, 1928, until October, 1930, when it had to be abandoned because of obliteration of the pleural cavity. Following the cessation of pneumothorax, a flare-up occurred, and he was referred to Montefiore Hospital for surgical treatment. Thoracoplasty was performed in March, 1932, and at present a marked collapse of the right lung following both an anterior and posterior costectomy is the result. However, the roentgen picture reveals the fact that the cavity remains open and the sputum is still positive for tubercle bacilli. The patient is still at the sanatorium and, though afebrile, he continues to cough, expectorates copiously and is unfit for work.

CASE 11.—S. D., a man, aged 23, was admitted to the sanatorium on March 12, 1930. His condition began in December, 1929, with an exudative lesion in the left lung. Pneumothorax was induced and continued for fifty-four weeks but had to be discontinued because of obliteration of the pleura. The patient was discharged as "quiescent," because for many months no marked constitutional symptoms were observed. He worked part time in the Altro workshops. Though no pronounced symptoms of progression were evident, he was urged to submit to surgical treatment.

Thoracoplasty was performed in several stages from January to March, 1932. No disabling symptoms were present before the operation, and none occurred subsequently. He was referred to the sanatorium for convalescence. At present, following an anterior and posterior thoracoplasty there are signs of an infiltrative lesion of the left upper lobe, and though the cavity appears smaller, he again has annoying symptoms; he coughs and expectorates. In fact, he has the same symptoms he had before the operation. He was more or less disabled by intensely chronic phthisis and remained so after the surgical operation. He was doing part time work at the Altro shops before the operation; he has been unfit to work since the surgical intervention.

CASE 12.—E. B., a man, aged 20, had a bronchopneumonic onset in March, 1929. He did well in the mountains for a while, but in April, 1931, had a hemorrhage, and pneumothorax was induced on the left side and continued until August, 1931, when it was discontinued because of a complicating pleural effusion. Thoracoplasty was performed in September and October, 1931, in an attempt to collapse the cavity. Since the operation he has felt well, but the cough and expectoration have continued. At present, physical signs reveal a thoracoplastic collapse of the left side, with the cavity still open and a fibronodular lesion on the right side with many consonating râles heard in the upper lobe. He is still taking "the cure" at the sanatorium. On Feb. 3, 1933, the sputum was found to be positive. The patient's condition is classified as "quiescent," as it was before the thoracoplasty, and he is unable to work. The pulmonary cavity is clearly visible on the roentgenogram.

CASE 13.—S. N., a woman, aged 24, was admitted to the hospital on Feb. 1, 1926, with an exudative lesion involving the lower lobe of the left lung and a productive lesion at the apex of the right lung. For over two years she had several episodes of exacerbation with long periods of remission. In August, 1928, pneumothorax on the left side was induced. However, the cavity in the upper lobe was not collapsed by the pneumothorax; symptoms of activity continued, and her condition was still considered progressive.

The first stage of thoracoplasty was done on Nov. 5, 1930. Four of her ribs were resected. The immediate postoperative condition was good. On November 19, the second stage, resection of the remaining ribs was completed. Within two weeks it was noted that while the intensity of the cough had not diminished, the



expectoration had become less. For the ensuing year there were exacerbations and remissions of the febrile course similar to those observed before surgical intervention.

In an attempt to control these symptoms and to secure better collapse of the cavity of the upper lobe, a supplementary anterior costectomy was performed on Feb. 5, 1932, the four upper ribs being removed.

On April 19, 1933, examination revealed that constitutionally there had been no change in the patient's condition since the anterior costectomy. She still coughs and expectorates, although she is afebrile; she is in the hospital suffering from symptoms of chronic phthisis, and unfit to do anything requiring exertion.

#### BILATERAL ACTIVE LESIONS

In several instances we have had thoracoplasty performed on patients with bilateral active lesions. There are cases in which one lung has an extensive cavitary lesion secreting a considerable amount of sputum, while in the contralateral lung there are fibroid changes, which may be considered sclerotic or at most quiescent. It is remarkable that only rarely is activity or extension of the lesion in the contralateral lung responsible for failure of the thoracoplastic operation. It has been our experience that when activity of the disease manifests itself after a thoracoplastic operation, it is due to a newly appearing lesion in the contralateral lung, most frequently in the midzone or even in the lower lobe, or to flaring of the lesion in the side operated on, which becomes progressively active, caseation and liquefaction taking place in the tissues that were hitherto quiescent. In these cases the patient, afebrile before the operation or having but a slight subfebrile temperature, suffers from high fever, which at first is considered the usual postoperative flare, but continues for weeks till a fatal termination of the case.

CASE 14.—D. R., a woman, aged 23, had pulmonary tuberculosis in 1922, remained at home for eighteen months, and then was admitted to the sanatorium in August, 1924. Therapeutic collapse of the left lung was performed in 1924, with fair initial results. However, she had a relapse of her symptoms in 1925 and went to another sanatorium for three months, but was discharged because the lesion was considered progressive. She remained in a mountain resort for several months, and then returned to the sanatorium of Montefiore Hospital in August, 1927, remaining until April 2, 1928, when she was transferred to the hospital. On this admission we found an extensive fibrocaceous and cavitary lesion in the left lung, a partial pneumothorax and a thickened pleura with a serous effusion, which soon absorbed. She suffered from fever, severe cough, copious expectoration, weakness, night sweats and loss of weight. On May 24, the first stage of a thoracoplasty was performed. She suffered a severe febrile reaction, and signs of involvement of the contralateral lung appeared. The fever subsided somewhat, and on May 31 the second stage was done. Surgical shock ensued. She appeared to be somewhat improved for the next few days, but six days after the second stage pulmonary edema developed and death occurred.

CASE 15.—F. R., a woman, aged 23, was admitted to the hospital in October, 1929, with a history of tuberculosis of one and a half years' duration. She was in

a municipal sanatorium for six months, where she did quite well until four months before this admission, when a febrile condition developed. On her admission to Montefiore Hospital we found a fibrocaceous involvement of the entire right lung, with cavitation in the upper lobe. A therapeutic pneumothorax was induced on October 29. A pleural effusion developed within three months, but she appeared to be doing fairly well. Pneumothorax therapy was continued for two years, but the collapse of the lung was never complete; a large cavity in the lower lobe remained open, and the pleural effusion persisted. Phrenicectomy was performed on June 25, 1931, but this had no favorable effect on the symptoms. On November 18, the first stage of a thoracoplasty was performed. One and a half hours after operation, surgical shock developed with cyanosis, a fall in the temperature of the extremities and other symptoms. In spite of vigorous stimulation, the patient died three hours after the operation.

*Autopsy* (Dr. D. Perla).—The anatomic diagnosis was: induced pneumothorax and phrenicectomy, right side (clinical); recent paravertebral thoracoplasty on the right; chronic pulmonary tuberculosis with cavity formation in the right lung; atelectasis and fibrosis of the right lung with bronchiectasis; tuberculous pneumonia of the right lower lobe; pleural effusion on the right side, and tubercles in the spleen.

Examination of the lungs showed the right to be shrunken to one half the size of the left and very firm. The anterior and lateral surfaces were covered by a markedly thickened pleura which measured from 1 to 2 mm. The upper lobe was reduced to a little more than the size of a large plum. It was deeply anthracotic and fibrotic, containing a few small areas of collapsed pulmonary tissue and a number of areas of caseous material, in places breaking down to form cavities into which bronchi could be traced. In the midportion of the lung laterally there was a cavity the size of a hen's egg, which was filled with buff-colored material and was lined by a shaggy caseous membrane. Below this there was a tuberculous pneumonia.

CASE 16.—H. V., a man, aged 36, was admitted to the hospital on March 25, 1927, with a history of having had an operation for ischiorectal abscess three years previously, followed by "pneumonia," which was later diagnosed as tuberculosis. On admission, we found a far advanced chronic pulmonary tuberculosis, fibrocaceous in type, involving the entire right side, with cavitation and thickened pleura. The course was febrile, and the patient was becoming progressively worse. Thoracoplasty was performed, the first stage on November 6, and the second stage on November 16. Following this, bronchopneumonia developed on the left side with pulmonary edema, and the patient died on November 21.

*Autopsy* (Dr. Perla).—The pleura of the left lung showed extensive sheetlike thickening throughout. Numerous small, fibrotic, discrete, conglomerate tubercles showed miliary distribution. There was nontuberculous bronchopneumonia of the lower lobe. The right lung was of a firm, nodular consistency. At the apex and at the base there were occasional discrete, conglomerate tubercles. Near the pleural surface was an area of encapsulated and slightly necrotic caseous material, 7 mm. in diameter. The cavity had a yellowish-white, purulent lining and a fibrous wall. The lower lobe showed another large cavity, having a firm, fibrous wall and a thick, dull-grayish lining. The remainder of the pulmonary tissues between the cavities and in the apex above showed marked fibrosis.

CASE 17.—M. F., a woman, aged 29, was admitted to the hospital on April 10, 1930, with a history of an insidious onset. In 1926, she was in a sanatorium for a year; subsequently she was successively in two hospitals for advanced tuberculous

disease. Eight attempts were made to induce a pneumothorax, with little if any benefit. On admission we found an extensive fibrocaseous lesion with cavitation in the left upper lobe and marked pleural thickening. The right lung was apparently normal. Under observation, it was found that the temperature ranged persistently around 100 F., and cough, expectoration and weakness were present. On November 19, a left phrenicectomy was done. The result was paralysis of the left vocal cord, but practically no elevation of the diaphragm. On Jan. 8, 1931, another attempt to paralyze the diaphragm was made, which proved futile. On February 4, the first stage of thoracoplasty was performed. Fever as high as 104 F. developed, and the patient complained of severe pains in the operative region. This febrile reaction continued for a month, finally becoming hectic, and the patient died on March 11.

*Autopsy* (Dr. Perla).—The anatomic diagnosis was: chronic bilateral pulmonary tuberculosis with cavity formation, tuberculosis of the large intestines and bronchopneumonia of the right lower and middle lobes.

In the left lung the pleura was considerably shrunk, thick and covered with thin fibrous sheets. The upper half of the upper lobe was replaced by a single large cavity with a rather smooth grayish wall. The remainder of the lung was atelectatic, fleshy and contained many fibrocaseous nodules.

The right lung showed nontuberculous bronchopneumonia.

CASE 18.—S. B., a man, aged 26, was admitted to the hospital on July 13, 1930, with a history of cough, fever, hemoptysis and emaciation for one year. He spent several months in the mountains in 1929, but after a slight initial improvement, the disease again became progressive. In April, 1930, phrenicectomy was performed at another hospital, and was promptly followed by paralysis of the vocal cords. On his admission to Montefiore Hospital, we found an extensive bronchopneumonic type of infiltration throughout the right lung. The right side of the diaphragm was normal, apparently unaffected by the attempted phrenicectomy. Thoracoplasty was performed in two stages on Jan. 21, and Feb. 19, 1931. Following the second stage, the patient went into severe postoperative collapse. Subcutaneous emphysema complicated the clinical picture. Two days later he had a brisk hemorrhage. Seven days postoperatively, the temperature dropped below normal, and the emphysema disappeared. He continued to expectorate blood-streaked sputum and had several copious hemorrhages during the next four months. He died from exsanguination and cerebral anemia on July 16, 1931.

*Autopsy* (Dr. Perla).—The anatomic diagnosis was: chronic bilateral pulmonary tuberculosis with a cavity in the right lung, bronchiectasis of the right lung, chronic passive congestion of the liver and spleen and fatty metamorphosis of the liver.

CASE 19.—F. H., a woman, aged 34, was admitted to the hospital on Feb. 25, 1931. Four years previously, after the birth of her second child, she noted blood-streaked sputum. She was reassured by her physician, who considered it of trifling significance. Two and a half years later, symptoms of active tuberculosis developed. In September, 1929, she went to Denver, where a left-sided phrenicectomy was performed. Therapeutic pneumothorax was attempted, but failed because of pleural adhesions. She was admitted to the sanatorium on Aug. 20, 1930, where the course of the disease was progressive. She was transferred to the hospital for thoracoplasty. On her admission we found a far advanced exudative lesion involving the entire left lung with a giant cavity in the upper lobe. On March 21, 1931, thoracoplasty was performed. For the next two months, she continued febrile. One month later, a copious hemorrhage occurred. Clinical and roentgen examination

three months postoperatively showed good collapse of the lung, but there remained a draining sinus in the lower end of the operative wound. She became subject to a psychosis and was transferred to another hospital. She died on Nov. 3, 1931, with definite evidences of amyloid nephrosis, nonprotein nitrogen amounting to 48 mg. per hundred cubic centimeters of blood, edema of the leg and face and ascites. Examination of the urine during her stay at Montefiore Hospital had given negative results.

We have seen from the clinical and roentgenologic evidence presented in the histories of the preceding cases that thoracoplasty does not collapse cavities in the lungs. At most, their size is reduced more or less. In the following cases this fact is confirmed by autopsy.

CASE 20.—L. R., a woman, aged 42, was seen on May 16, 1928, with a history of an insidious onset two and one half years previously. In April, 1927, an attempt was made to create a pneumothorax on the right side, but no collapse of the lung resulted because of pleural adhesions. The case was of the common chronic recrudescient type with occasional episodes of fever. Thoracoplasty was done in three stages from December, 1927, to February, 1928. The patient bore the operations well, and the wound healed nicely. Three weeks after the last operation a sinus opened in the wound discharging pus. The patient was transferred to Montefiore Hospital with symptoms of active tuberculosis, persistent cough and expectoration, fever, etc.

Physical examination in January, 1929, revealed that there was still evidence of active tuberculous disease in the lung and a discharging sinus externally. The cavity in the right upper lobe remained open.

For the ensuing eighteen months she grew progressively worse. The disease ran an active febrile course. There were marked gastro-intestinal symptoms of cramps and diarrhea. The liver was enlarged to 4 inches (10.16 cm.) below the costal margin, and there was albumin in the urine, three plus. Generalized edema appeared. The patient died on Feb. 16, 1931, three years after the operation.

*Autopsy* (Dr. Perla).—The anatomic diagnosis was: chronic bilateral pulmonary tuberculosis with cavitation in the right upper lobe, tuberculosis of the large and small intestines and of the suprarenal glands, a chronic tuberculous extrapleural-intrathoracic abscess and severe amyloidosis of the liver, spleen, kidneys and thyroid.

The left lung was voluminous, with small fine nodules palpated throughout. On section, a small cavity was found in the apex.

The lower lobe of the right lung was free and emphysematous with discrete tubercles. In the region of the lower lobe the parietal pleura appeared thickened. This thickening was due to a dissection of the parietal pleura from the wall of the chest by large amounts of purulent fluid which were released by puncturing the parietal pleura. The abscess cavity revealed between the parietal pleura and the wall of the chest extended throughout the entire right side of the chest anteriorly and posteriorly. In the posterior region at the second rib this abscess cavity communicated by a fistula with the sinus opening anteriorly. The right upper lobe was firmly adherent to the wall of the chest, so that on removal there was considerable tearing and a large part of the right lung was left attached to the thoracic wall. Most of the right upper lobe was replaced by a large oval cavity measuring 12 cm. in its longest diameter. The remainder of the parenchyma was fibrotic and contracted and contained fibrotic tubercles.

CASE 21.—A. L., a man, aged 23, was admitted to the hospital on Oct. 14, 1924, with a history of active tuberculous disease of one year's duration. Examination revealed an extensive infiltration of the left lung with multiple cavitation; the right lung was apparently normal. Thoracoplasty was done in two stages on Oct. 6 and Oct. 21, 1926, shortly after the patient's admission. As soon as the wound healed he was sent to the country. Our next information concerning him is of July 1, 1932, almost five years later, and is to the effect that he died at Mount Sinai hospital in May, 1932. The autopsy there showed: generalized amyloidosis, disseminated tuberculosis of both lungs, caseous tuberculosis of the right suprarenal gland and pulmonary atelectasis and bronchiectasis of the left lung.

CASE 22.—S. W., a woman, aged 28, was admitted to the hospital on Oct. 5, 1930, with a history of tuberculous disease of six years' duration. A futile attempt was made to induce a pneumothorax. Phrenicectomy was then performed, and she improved for a short time. When the patient was examined on admission we found an exudative lesion involving the entire left lung and pleura, with multiple cavitation. There were signs of a fibrotic lesion of the apex of the right lung and sinistocardia. On fluoroscopy, paradoxical movement of the diaphragm was evident.

Thoracoplasty was performed on October 19, and the immediate response to the resection of the upper five ribs was excellent with an amelioration of the constitutional symptoms. The second stage was fairly well borne, and within a month cough and expectoration had diminished. These good results continued for three months, when signs of activity of the lesion reappeared. Fever and wasting continued with edema of the lower extremities, but there was no evidence of hepatic or splenic enlargement. Death occurred on Dec. 1, 1931, one year after the operation.

*Autopsy* (Dr. Peria).—The anatomic diagnosis was: postoperative phrenicectomy and thoracoplasty of the left lung, chronic bilateral pulmonary tuberculosis with cavity formation of the left lung, atelectasis and fibrosis of the left lower lobe, caseous bronchial pneumonia of the right lung and amyloid spleen.

The right lung showed tuberculous pneumonia. The left lung was one half the size of the right. The pleura was thickened. In removal, several cavities were opened and these exuded buff-colored, creamy material. Most of the upper lobe was so replaced by a series of intercommunicating cavities that practically no parenchyma was left. The lower lobe was markedly contracted owing to atelectasis and fibrosis.

CASE 23.—I. L., a man, aged 20, was admitted to the hospital on Oct. 20, 1924, with a history of tuberculous disease of six weeks' duration. A therapeutic pneumothorax was induced on November 24, collapsing the left lung. The patient responded favorably, but because of pleural adhesions further insufflations had to be discontinued on March 5, 1925. Symptoms of active disease recurred. On May 9, left-sided thoracoplasty was done. After the first stage, the patient's condition became worse and the constitutional symptoms markedly accentuated. The pulse became very rapid and feeble; the temperature continued to run between 101 and 102 F.; cough and expectoration were unabated. The disease continued active and progressive, and death occurred on October 9, four months after the operation.

CASE 24.—A. B., a man, aged 26, was admitted to the hospital in July, 1924, with a history of active tuberculosis of two months' duration. A left-sided pneumothorax was performed at our sanatorium in August, 1924. He remained there for two years, feeling somewhat improved, but the fever persisted. From thence he went to the mountains, where he found no relief. He returned to the hospital on Aug. 10,

1927, seeking surgical treatment. A left-sided thoracoplasty was done on October 7. The operation had no beneficial effects, and the patient left the hospital on Feb. 25, 1928.

He remained at home for three months, bedridden, with a low grade fever. When he was readmitted on May 19, we found his general condition poor; the left lung (thoracoplasty side) showed an extensive active fibrocaceous lesion with multiple cavities. The upper lobe of the right lung showed signs of parenchymatous infiltration. On June 25, spontaneous pneumothorax developed, collapsing the right lung. The patient committed suicide the same night, stabbing himself with a knife.

*Autopsy* (Dr. Perla).—The anatomic diagnosis was: chronic pulmonary tuberculosis with cavity formation of the left upper and right lower lobes, pneumothorax and bronchopleural fistula of the right lung, penetrating wound of the left side of the chest, tuberculous enteritis and laryngitis, amyloid disease (generalized) and healed thoracoplasty (left).

The pleura of the left lung presented extensive thickening. The entire upper lobe and the lateral portion of the lower had a nodular consistency. On section, a fibrous cavity about 4 cm. in diameter was found in the upper lobe laterally and anteriorly. It had a smooth yellow lining and was filled with blood. The surrounding parenchyma in almost the entire upper lobe had a peculiar gelatinous, grayish, fibrous appearance through which were scattered small foci of inspissated caseous material and areas of nontuberculous atelectasis. The lower lobe presented a similar appearance. The organs were positive for amyloid.

Case 25.—A. T., a man, aged 36, was admitted to the hospital on July 26, 1926, with a history of tuberculous disease for two and one-half years. He suffered several rather profuse hemorrhages. We found signs of involvement of the entire right lung and pleura. The lesion in the left lung was apparently inactive. After a rest for a month, he felt somewhat better, although the temperature still remained elevated and the cough and expectoration persisted.

Right-sided thoracoplasty was performed on Sept. 8 and Oct. 25, 1926. After the second stage he appeared to be critically ill with symptoms and signs of pulmonary edema, requiring vigorous treatment. Though he recovered from this episode, the symptoms of active and progressive tuberculosis continued unabated. He died on June 23, 1927, nine months after the operation.

CASE 26.—I. M., a woman, aged 27, was first admitted to the hospital on July 8, 1926, with a history of cough and hemoptysis and an intermittent febrile condition of a chronic recrudescence type, of eight years' duration. Pneumothorax had been attempted several times, but the results were unsuccessful for the usual reasons.

Examination on admission revealed an extensive right-sided lesion with cavitation and slight fibrosis in the apex of the left lung.

Thoracoplasty on the right hemithorax was performed in two stages on July 12 and 27, 1926. Following the second stage the patient went into collapse on the operating table. She recuperated after a blood transfusion of 500 cc. Her general condition improved to such a degree that she left the hospital one month after the operation. She remained at home, where the improvement continued and she gained 23 pounds (10.4 Kg.) in weight within four months. But she was never completely free from symptoms of active disease. An acute exacerbation occurred; the temperature rose, and symptoms of progressive phthisis were manifest. She was readmitted to the hospital on Dec. 19, 1926, and a right-sided phrenicectomy was performed. But the disease continued to run a febrile course unabated. Climatic treatment was then tried. For the next three years she continued the

"cure" in the mountains, growing worse until she died in June, 1929. During the three years between the thoracoplastic operation and death, she was not free from symptoms of active pulmonary tuberculosis.

#### HEMOPTOIC CASES

Among the patients with quiescent tuberculosis there are certain ones who are characterized by paucity of constitutional symptoms for months or years; they have no fever, cough but slightly, maintain their body weight, and are fit for many sorts of occupations requiring no excessive muscular exertion. But they have hemorrhages now and then. In some, the hemorrhages are slight, but sufficient to frighten them and those around them; in others, the hemorrhages are copious, even threatening, appearing at irregular intervals and lasting for days or weeks. These patients may be disabled during the long periods when they do not bleed, because they always fear lest, when least expected, a hemorrhage may appear. In hospitals for patients with advanced consumption there are many patients of this type occupying beds which are needed for persons with the disease in active form. Often a few days or weeks after discharge, this complication brings them back to the wards. Eight patients of this type were selected by us for thoracoplasty, with a view of preventing recurring pulmonary hemorrhages. Typical is the following:

CASE 27.—R. W., a woman, aged 20, was admitted to the hospital on June 11, 1923. She had been sick for three years with a fibrocaceous lesion involving the greater part of the left lung with a large excavation in the upper lobe. The most annoying symptom was pulmonary hemorrhage recurring at irregular intervals, at times very copious and threatening. The general condition was fairly good, but because of the recurrent bleeding the left lung was collapsed in June, 1923, and a satisfactory pneumothorax was created which was sustained for two years, when obliterative pleuritis prevented continuation of insufflations. She continued to do well, even becoming somewhat obese, but with reexpansion of the lung the hemorrhages recurred. With a view of preventing bleeding, thoracoplasty was performed on Dec. 17, 1925. She reacted badly to the first stage of the operation, necessitating hypodermoclysis of 1,000 cc. of saline solution. She recuperated, and on Jan. 6, 1926, the second stage of the operation was done. The wound healed soon, and we sent her to the sanatorium where she remained for two years, bleeding slightly now and then. After her discharge from the sanatorium she again had an exsanguinating hemorrhage lasting a week. However, the constitutional symptoms have been in abeyance since the operations; she coughs less and her sputum has been free from demonstrable tubercle bacilli. She has been employed at the Altro shops doing four hours of work a day as a seamstress. She still expectorates blood now and then, but has no severe hemorrhages. A physical and roentgen examination made recently shows that while the left lung is fairly well collapsed, there are unequivocal signs of an excavation in the upper lobe of the left lung.

CASE 28.—B. S., a man, aged 30, was admitted to the sanatorium on Feb. 11, 1926, with a history of an insidious onset, followed in three months by a brisk hemorrhage. A left-sided pneumothorax was induced, which was effective in

stopping the bleeding and allaying the fever. The lung was left collapsed for fourteen months, when we felt safe in employing the patient as a technician in the x-ray department; he was engaged in this occupation for one and a half years, when a relapse occurred, which caused his readmission to the hospital. Continuous fever and recurrent hemorrhages necessitated radical treatment.

Thoracoplasty was performed in three stages. The upper three ribs were resected at the first stage, Aug. 19, 1929, and the patient returned from the operating room in a poor condition, with rapid and weak pulse and cold and clammy skin. He rallied and was fairly comfortable the next day. For the ensuing fourteen months he remained in the hospital, practically always confined to bed, but his general condition improved gradually; he gained in weight. However, he still suffered from recurrent hemorrhages. We then transferred him to the sanatorium, where he remained for nine months. At the time of his discharge from there, July 11, 1932, he was afebrile, fairly well nourished but not rehabilitated to the degree that he could be considered cured. Following his operations, therefore, he was compelled to remain hospitalized for over two years, and he is still not well enough to work steadily for any considerable time. But he does not bleed as often or as profusely as before the operation, though he continues to be tuberculous.

CASE 29.—M. L., a woman, aged 21, had hemoptysis one year before admission, in September, 1925, when an extensive and cavitary involvement of the left lung was found. The right lung was normal. Pneumothorax was done on Nov. 4, 1925, to control bleeding and fever, with excellent results. Pleural effusion noted on December 4 brought about abandonment of this therapy, and nine months later the patient was transferred to the sanatorium with but slight constitutional symptoms of activity. Within a month she again became afebrile and suffered from recurrent hemorrhages, which were quite copious. With a view to control the hemorrhages, thoracoplasty was started on Sept. 10, 1926, and completed on Nov. 17. Three months later her condition was excellent, both local and general. She then left the hospital. During the course of the next two years she reported the recurrence of hemoptysis, cough and expectoration, though her general condition remained fair. Following this period an acute febrile attack suddenly developed followed by a copious hemorrhage. She was admitted to Bellevue Hospital where a supplementary and more extensive resection of ribs was performed. Her general condition improved after the operations, and she was readmitted to the sanatorium, where she remained for ten months. Her condition at present is considered quiescent. She attends the outpatient tuberculosis clinic. She still suffers from symptoms of chronic and active tuberculosis and is not fit for work.

CASE 30.—M. M., a man, aged 19, was admitted to the hospital on May 20, 1925, with a history of an acute hemoptotic onset three weeks previously and fever mounting to 105 F. Physical signs revealed an extensive caseous infiltration of the entire left lung. A pneumothorax was created on the day of admission. No marked beneficial results were obtained by this treatment so far as the febrile and toxic symptoms were concerned, and the pneumothorax was abandoned within three months. During the following three months the temperature subsided; the patient's general condition improved, and he was sent to the country sanatorium for convalescence. During the first seven months of his stay there he did very well and gained 15 pounds (6.8 Kg.) in weight. Because of recurrent and uncontrollable hemorrhages, he was transferred to the hospital for thoracoplasty. Examination then showed extensive involvement of the entire left lung and pleura with an enormous excavation of the upper half. On Aug. 3, 1926, the first stage, which was being performed under local anesthesia, had to be abruptly stopped because of signs of cardiac failure. The operative series was completed one month later. In



October, the following note was entered: "Because of tachycardia, fatigability and emaciation this patient requires further strict rest treatment even though the temperature is normal." Two months later he went home to continue the rest treatment. He has been continuously under observation for seven years. We find that he is unable to work at anything. He has frequent febrile exacerbations and hemoptysis and is dyspneic. Of late he has symptoms of tuberculosis of the larynx.

CASE 31.—R. L., a man, aged 35, was seen in September, 1927, with a history of an insidious onset. He remained in the sanatorium six months and was discharged afebrile with a gain of 17 pounds (7.7 Kg.) in weight. At home for several months he suffered from copious hemorrhages. A right-sided hemostatic pneumothorax was induced and continued for eight months. Insufflations were discontinued in January, 1929, because of a pleural effusion. The patient remained well until May, 1929, when hemorrhages lasting a week or more and recurring at irregular intervals caused him to apply for readmission.

When he was readmitted, March 5, 1930, we found an extensive fibrocaseous lesion with a cavity in the right upper lobe and a thickened pleura. With the exception of recurrent hemorrhages, the lesion was not productive of serious constitutional symptoms and showed no tendency to progression. The surgical staff characterized the case as "ideal" for thoracoplasty. This was done with no immediate untoward operative results. Four months later it was noted that a fairly good collapse of the lung had been attained and, as before the operation, the temperature was normal; but the pulse was rather rapid, and the patient was dyspneic. He still expectorates blood-streaked sputum occasionally, though there have been no large hemorrhages. On physical and roentgen examination the cavities are still evident. For fifteen months he has remained in the hospital because we have considered him unfit for discharge, and during the past three months his fever has mounted and tuberculosis of the larynx has developed.

CASE 32.—B. K., a woman, aged 35, was admitted to the hospital on May 10, 1919, where she remained for nine months. Right-sided pneumothorax was maintained for five months, during which period a contralateral pleural effusion developed. The patient's general condition improved to such a degree as to render her fit for discharge. She felt fairly well for four years. Then fever, cough, expectoration and recurring hemorrhages reasserted themselves. The examination on admission, March 16, 1926, showed a large cavity in the right upper lobe with a thick pleura. Thoracoplasty was advised mainly with a view of preventing the recurring hemorrhages.

Following the first stage of the operation on April 17, the patient had a severe reaction, and for five days the severe hemorrhages and high fever, 104 F., were menacing. However, six days later her general condition improved so that the second stage was done. This was followed by infection of the wound. The post-operative course was again very stormy, infusion and transfusion being necessary. A toxic psychosis developed, the temperature rose to 105 F., and signs of an active lesion were found in the contralateral lung.

However, after she had remained in the hospital under routine treatment for another year, her general condition was found improved, though she still suffered from active tuberculous disease. Efforts to trace her have proved unavailing.

CASE 33.—F. L., a woman, aged 36, has a clinical history which embodies almost the entire natural history of chronic pulmonary tuberculosis, illustrating the benefits to be expected from current therapy, old and new. In 1918, dry pleurisy developed in the right side of the chest with a mild febrile reaction. The patient spent a

summer in the mountains convalescing. She recovered her health and felt well for two years. Constitutional symptoms of tuberculosis then reappeared; sputum was found positive for tubercle bacilli. She went to a sanatorium, remained there for one year and was discharged greatly improved. She married soon after her discharge in 1921. In 1923, the only symptoms noted were cough, slight expectoration and easy fatigability. To overcome these symptoms a full course of tuberculin therapy was administered by a private physician from Nov. 14, 1923, to April 2, 1924, with no detrimental results but no startling improvement. Thence until 1928 she was ambulant and afebrile with occasional expectoration of blood-streaked sputum most marked at the menstrual period. That year profuse exsanguinating hemorrhages developed, and an emergency hemostatic pneumothorax was performed as a life-saving measure. In spite of the old history of pleurisy and the chronicity of the lesion, collapse of the lung was easily obtained and the bleeding stopped. The ensuing year she felt well, but fluid appeared in the pleural cavity and insufflations had to be abandoned. She then again began to bleed; most often there was slight blood-streaked sputum, but occasionally, quite profuse hemorrhage. This continued off and on until December, 1930. At that time the patient pleaded that something more heroic be attempted to remove her constant fear of recurring hemorrhages, even though none had been very severe since 1928. She herself suggested thoracoplasty. Examination revealed an extensive fibrotic but cavitary lesion in the upper lobe of the right lung, a markedly thickened pleura and fluid in the pleural cavity.

The first stage of thoracoplasty was performed on Dec. 9, 1930, with no untoward results. The second stage was followed by a stormy postoperative course, accompanied by a high fever. Subsequently an infection of the wound developed. But she was discharged to her home two months later with all wounds healed, to "build up" before the final stage was to be done. She was readmitted one month later, and the third operative stage was performed. Blood-streaked sputum again was present, and her general condition left much to be desired. A supplementary operation was decided on. A more extensive resection by the axillary route was performed, with no untoward postoperative reaction. She now has a small draining sinus, signs of an active lesion in the lung and coughs up blood at irregular intervals. It cannot be said that the repeated surgical operations have benefited her to any degree, because she is still tuberculous and still bleeding.

CASE 34.—S. B., a man, aged 26, was admitted to the hospital on June 18, 1928, with a history of an acute febrile onset three months previously. Examination showed an extensive exudative infiltration of the left lung. Pneumothorax was performed with immediate good results. A few months later fluid developed in the pleural cavity, but the patient continued to do well. Ten months later fever and recurrent hemorrhages appeared. With a view of preventing the hemorrhages, thoracoplasty was done on April 2, 1930. The immediate reaction was unfavorable. The disease became acutely active, and death occurred on June 7, 1930.

*Autopsy* (Dr. Perla).—The anatomic diagnosis was chronic bilateral pulmonary tuberculosis; thoracoplasty on the left side, nine ribs; gangrene of the small intestines; acute fibrinous peritonitis, and amyloidosis of the spleen and suprarenal gland.

The left lung was smaller than the right. The left pleura was covered by dense fibrous adhesions. The lung was collapsed and firm. On section, it was riddled with large and small communicating cavities. The intervening parenchyma was nonaerated and had a red meaty appearance. The right lung was fairly normal.

## TUBERCULOUS PYOTHORAX

Tuberculous pyothorax, irrespective of its mode of origin, has been a bugbear in phthisiotherapy. All efforts at controlling this complication have been either ineffective or altogether harmful. Our experience has been that it is best to apply palliative, but strictly conservative measures. We have tried various forms of thoracotomy, puncture and drainage, injections of antiseptics or dyes and irrigations of the pleural cavity and have not been impressed with the results. Of course, in exceptional cases patients have been going about with chests filled with pus for many years; one for over ten years. Some even pursued more or less active lives and engaged in remunerative occupations while the pleural cavity was filled with pus. But these are exceptional; the vast majority of this class of patients fail irrespective of the treatment and succumb sooner or later because of the toxemia, extrathoracic tuberculous lesions, especially of the larynx and intestine, or amyloidosis.

Of the ten patients with pyopneumothorax submitted to thoracoplastic operation at the Montefiore Hospital, four are dead, two are in the hospital very ill, three attend the follow-up clinic with draining sinuses and one is well and working at a part time job.

In six cases the pyothorax was a sequel of therapeutic pneumothorax. The pneumothorax had proved quite beneficial for a period of from one month to five years before the onset of this complication. Two cases followed spontaneous pneumothorax; one was a sequel of simple, "idiopathic" pleurisy with effusion and one of a pleural effusion in a tuberculous patient.

The clinical histories of these ten cases follow:

CASE 35.—S. Z., a woman, aged 27, was admitted to the hospital in November, 1925, with a history of pulmonary tuberculosis of ten months' duration. She was in a sanatorium where an artificial pneumothorax was induced on the left side. Within a few months a purulent pleural effusion was found and tapped repeatedly, but the febrile condition continued unabated, pus reaccumulating after each tapping. Three months before admission to Montefiore Hospital, rib resection with thoracotomy and drainage by tube were performed. The constitutional symptoms abated considerably during the first weeks at the hospital. But there remained a bronchial fistula and a draining sinus with concomitant symptoms.

On December 9, the first stage of thoracoplasty was performed. The immediate postoperative reaction was quite severe, with rapid, thready, weak pulse. However, four weeks later the patient had recovered sufficiently to warrant further rib resection. The second stage was performed on Jan. 6, 1926, and the third on February 3. On April 21, the patient still coughed up considerable quantities of purulent material, and there was profuse discharge from the wound. In other words, the pus continued to form and drain through the bronchi, as well as through the wall of the chest.

Two supplementary operations were performed in an attempt to obliterate the sinus tract by more extensive rib excisions. The patient left the hospital in July,

1926, still coughing and with pus draining from the sinus track and with sputum positive for tubercle bacilli.

Subsequent reports from the surgeon who has since taken care of her were received in August, 1919, as follows: "The patient was seen several months ago. Her general condition is satisfactory. The wound is apparently healed. Pains from time to time may be referable to a collection of fluid. The patient has gained in weight and strength."

In 1932, the report is to the effect that she feels well and keeps house for the family.

CASE 36.—E. D., a woman, aged 20, was admitted to the hospital on Oct. 3, 1927, with a history of tuberculosis of one year's duration. Five months later a febrile "pneumonic" attack developed. A left-sided pneumothorax was performed because the constitutional symptoms indicated activity. The immediate results were considered favorable. An exudate appeared in the pleural cavity within three months, accompanied by an acute febrile reaction; 750 cc. of clear amber-colored fluid was aspirated. Many aspirations were performed subsequently because of symptoms of mediastinal pressure, but the fluid reaccumulated after each tapping.

Four months later, the fluid became purulent, and 1,500 cc. of pus was removed. Tappings were repeated for four months more, when a large cold abscess developed at the back of the left side of the chest just below the costal margin. During this period the patient appeared quite toxic, with fever of from 101 to 103 F.; the mediastinum was markedly displaced to the right, the liver extended to about 6 cm. below the costal margin, and the spleen was enlarged. A clinical diagnosis of amyloid lesion was made.

The cold abscess was incised, and a tube was inserted which passed through the sinus track and drained the empyema cavity. Following the establishment of external drainage, the patient improved markedly, and the constitutional symptoms abated. The liver and spleen likewise receded in size. After six months of drainage by tube, the clinical picture changed. There was now a discharge of approximately 75 cc. of pus daily. The patient was able to be up and about, wearing a modified colostomy bag to collect the pus. She was afebrile, felt well and gained 10 pounds (4.5 Kg.) in weight.

After another six months the pus in the left pleural cavity had been almost completely evacuated through the closed thoracotomy opening, and the lung on that side reexpanded. There was, however, a sinus track, and the drainage through the tube leading into the small pyothorax cavity had to be continued. The purulent discharge required a change of gauze twice daily. No symptoms of dynamic activity of the pulmonary lesion were present.

In January, 1930, eighteen months after the original incision for drainage, the surgeon suggested resection of the lower ribs in an attempt to obliterate the cavity and the sinus track. The ninth, tenth, eleventh and twelfth ribs and part of the roof of the empyema cavity were removed. The immediate postoperative reaction was favorable. Twelve days later four more ribs were resected. This time there was some postoperative shock, requiring an intravenous saline infusion. Six weeks after this the upper three ribs were removed with a view of attaining complete collapse of the lung. The patient left the hospital on April 27, 1931, with the sinus still discharging pus. She is at present ambulatory and feeling quite well. She is employed as a clerk, working four hours daily. But, as stated, the sinus in her chest has not closed. She still carries a drainage tube in the sinus track. If she attempts to go without the tube, pus accumulates and a febrile reaction occurs.

CASE 37.—M. K., a man, aged 26, was admitted to the sanatorium on Oct. 20, 1920, with a history of tuberculosis of three months' duration. In January, 1921,

an artificial pneumothorax was induced with good initial results. He left the sanatorium in 1922, and was cared for till 1927 in his home. A pleural effusion was noted in 1922, and in 1924 the fluid assumed a purulent character. However, this did not deter him from working as a salesman for four years, going to a private physician for pneumothorax insufflations. He felt well until Sept. 27, 1927, when he reentered the hospital because of an acute febrile attack.

On admission a far advanced pulmonary lesion together with a left pyopneumothorax was found. Six hundred cubic centimeters of pus was aspirated, and a few treatments with oil of gomenol were tried without improvement. The febrile course continued. Thoracotomy for drainage was tried on October 18, without any notable salutary effect. Then a three-stage thoracoplastic operation was performed, starting from below, on Nov. 10, 1927, Jan. 5, 1928, and February 5. After the third stage, the temperature mounted and necrosis of the upper end of the operative wound was noted.

Within six months the wound assumed a somewhat more satisfactory appearance, but the pus continued to drain and the patient was up and about. Since that time he has been cared for at the outdoor clinic and by the social service department. He still has a large sinus track; one can look through it as through a window and closely observe the granulations on the visceral pleura. Occasionally the wound bleeds. His pulmonary tuberculosis *per se* gives rise to but few annoying symptoms. He is unable to work and requires so much gauze for his dressings that he has become quite a costly patient.

CASE 38.—J. S., a man, aged 28, was readmitted to the hospital on Oct. 3, 1930, with a history of a left-sided tuberculous pneumonic process of four years' duration. He had received pneumothorax therapy for six months and had improved. He then stayed at home for two and a half years, where the therapy was continued. Because of complicating pyothorax one year before this admission, closed thoracotomy was performed at a hospital and then he was referred to our sanatorium. Under routine care he improved, was afebrile and ambulant and gained 12 pounds (5.4 Kg.) in weight, when suddenly a copious pulmonary hemorrhage occurred, following which his general condition became worse.

It was then decided in view of the exacerbation of the symptoms, the hemorrhage and the cavitary lesion in the left upper lobe, in addition to the long-standing pyopneumothorax, that a thoracoplasty should be tried.

After the first stage of the operation, performed on Dec. 3, 1930, there was no marked reaction. The second stage, ten days later, resulted in a stormy post-operative course. There was definite evidence of mediastinal flutter with marked shifting of the mediastinum to the right. Within a few days signs of extensive bronchopneumonia became evident in the contralateral lung. The course continued febrile during the ensuing five weeks. However, the patient recovered, and the twelfth rib was resected on Jan. 28, 1931. Finally a phrenicectomy was performed on March 11.

His general condition remained poor; he had lost 30 pounds (13.6 Kg.) since the operations and was very dyspneic on the slightest exertion. The right lung was vicariously emphysematous; the mediastinum shifted, especially during deep inspiration. With thoracoplasty a notable diminution of the left hemithorax and an immobilized diaphragm without paradoxical movement were attained. On the roentgen film a fine acinonodular infiltration throughout the right lung was seen, best explained as a result of the bronchogenic spread following the second stage of the operation. He had a discharging sinus and was very dyspneic. He went to the country to continue with the treatment.

On examination two years after the operation the following findings were recorded: a discharging sinus, dyspnea and signs of active tuberculous disease in both lungs with positive sputum. He looks fairly well and is able to be up and about the greater part of the day, but he is still unfit to engage in any gainful occupation because of cough and dyspnea.

CASE 39.—M. S., a man, aged 28, was admitted to the hospital on April 26, 1923. The onset of his condition was in 1922. In April, 1923, a spontaneous pneumothorax developed accompanied by high fever and a pleural effusion, for which he entered the sanatorium. He remained there eighteen months. Aspiration of fluid and replacement by air were practiced. He was discharged from there in fair condition in October, 1924.

For the next four years he was more or less symptom-free and worked. In April, 1928, a febrile reaction developed lasting five weeks, with pain in the left side of the chest, which was somewhat relieved by aspiration of the pus. In October, 1928, following repeated aspirations, fever became high and the pus began to point on the thoracic wall. A rib resection with drainage by tube was done, giving marked amelioration of the toxic symptoms. After one month the tube was removed and the wound healed, but fever reappeared shortly, to be assuaged when the wound opened spontaneously discharging a large quantity of pus. On Dec. 3, 1930, he was admitted to Montefiore Hospital with a draining pyopneumothorax and signs of activity of the pulmonary lesion.

On routine care and observation he did fairly well for four months, was afebrile and was gaining weight. There was a small pocket of pus discharging through a small sinus. The surgical consultant, however, insisted that radical surgical intervention was imperative.

In November, 1931, he made the following observation on the chart: "I think it is quite impossible for spontaneous cure to occur in this case. One must postulate an empyema cavity with tremendously thick walls and a large dead space. In my opinion such a chronic uncared for pyogenic pus will ultimately kill the patient and that will be a very sad sequel for a man who is apparently entirely cured of his pulmonary tuberculosis."

Accordingly, a partial thoracoplasty with unroofing of the entire lower part of the cavity was performed. A few days later a bronchial fistula became evident accompanied by continuous high fever. Signs of a new progressive tuberculous process were then found in both lungs. The wound drained imperfectly and had to be probed frequently. The febrile course continued for four months, and the patient was very weak and toxic, with marked anemia necessitating a blood transfusion. At present he presents the clinical picture of pyopneumothorax draining fairly well, and good evidence of amyloidosis.

CASE 40.—A. H., a man, aged 39, was admitted to the hospital on November 17, 1928. Tuberculosis developed in 1918, and he remained at Saranac Lake for one year with no notable improvement. Because of recurring hemorrhages, right-sided pneumothorax was done in 1919, which ultimately was complicated by pyothorax. In 1926, thoracoplasty followed by a phrenicectomy was performed at another hospital (1928, an empyema necessitatis). On admission, the patient showed evidence of pyopneumothorax, bronchial fistula and two draining sinuses in scars of the old thoracoplasty incisions. Weakness was marked. One year later he underwent a supplementary rib resection with a view to draining the pus from the pleural cavity.

At present the patient weighs 98 pounds (44.5 Kg.) after weighing 124 pounds (56.2 Kg.) originally, coughs and expectorates thick, yellowish sputum profusely

and presents evidence of chronic fibroid cavernous phthisis of the right lung together with a pyopneumothorax, large draining sinuses and bronchopulmonary fistula.

CASE 41.—H. A., a man, aged 20, was admitted to the hospital on June 4, 1924, with a history of an insidious onset eighteen months previously. A pleural effusion developed six months later. For this he was tapped several times before he entered the hospital. On admission, 1,100 cc. of purulent fluid was aspirated from the left pleural cavity. For several months the common oscillation of exacerbations and remissions was observed. He was relieved more or less by aspirations and pleural lavage. However, because of the marked toxic symptoms, surgical intervention was decided on. The seventh and eighth ribs were resected to obtain drainage. Some improvement was noted soon after the operation.

On April 8, 1925, the first four ribs were resected in paravertebral thoracoplasty. Six hours after operation, severe dyspnea and cyanosis developed. The pulse became weak and thready, and the patient died on April 10, with symptoms of heart failure.

At the postmortem examination, the left lung was found completely collapsed in the lower two thirds. The upper third was bound to the chest by dense inseparable fibrous adhesions. The visceral pleura over the lower half of the upper lobe and the entire lower lobe was markedly thickened and covered with a purulent layer.

CASE 42.—J. G., a man, aged 30, was admitted to the hospital in October, 1922, with a history of an insidious onset. At the sanatorium a right-sided pneumothorax was induced. He was discharged seventeen months later to go back to work, which he did. Pneumothorax insufflations were continued by a private physician until ten weeks before readmission, Aug. 27, 1927. The fluid became purulent, and a bronchopleural fistula developed. The left lung was apparently free from active disease.

Thoracoplasty was performed in several stages in November and December, 1927, but the postoperative course was unfavorable, with rather severe shock. Pus continued to drain from sinuses, about 200 cc. daily; cough, expectoration and weakness continued to be troublesome symptoms. The disease continued to run an active febrile course, and seven months later tuberculous pneumonia developed in the left lung, which proved fatal.

CASE 43.—G. P., a man, aged 33, was admitted to the hospital in October, 1923, with a history of an insidious onset. He remained at the sanatorium for five months, where he gained weight and improved generally. The only symptom on discharge in March, 1924, was cough. He worked as a clerk for four years more or less continuously. In October, 1928, febrile relapse occurred, and a purulent pleural effusion was found which had to be tapped repeatedly. He was admitted in July, 1929. He improved under routine treatment, became afebrile and was sent to the sanatorium. There he felt well until Jan. 14, 1930, when, because of a recrudescence of acute symptoms and high temperature, 104 F., he was transferred to the hospital.

Empyema necessitatis developed along the needle track of aspirations of a large pyopneumothorax. A resection of the ninth and tenth ribs was done, and a large amount of pus was removed, following which the fever decreased. Drainage continued through this opening, but a low grade fever persisted. Thoracoplasty was performed on June 11 and 25, 1930, in an attempt to obliterate the dead space. However, three months later high fever suddenly reappeared, and an area of fluctuation appeared under the healed scar. The wound was laid open and pus evacuated. He continued to do poorly and died on October 12.

*Autopsy* (Dr. Perla).—The anatomic diagnosis was: chronic pulmonary tuberculosis of the right lung and left lower lobe, thoracoplasty of the right side (recent), complete collapse of the right lung and amyloidosis of the liver, spleen and kidney.

The right lung was almost completely collapsed and was converted into a mass of deeply pigmented, very firm fibrous tissue. No reaction was present. The left lung was emphysematous.

Microscopic examination of the right lung showed the greater portion of the lung to be composed of anthracotic, vascular, rather cellular fibrous tissue. In addition two large areas of coagulation necrosis well encapsulated were present. Numerous calcium deposits were in this area.

CASE 44.—M. De, a man, aged 23, was admitted to the hospital on May 30, 1924, with a history of tuberculous disease of two years' duration. Spontaneous pneumothorax developed on the left side followed by pyothorax. In June, 1924, thoracoplasty was performed, with some immediate benefit, and the patient was transferred to the sanatorium. For three months he continued ambulant and felt fairly well. Retention of pus resulted in a fever of 103 F.; reestablishment of drainage ameliorated this symptom. He suffered several recurrences of the aforementioned cycle. In an attempt to overcome this, thoracoplasty was decided on. The first stage, done Jan. 31, 1925, was uneventful. Immediately after the second, February 21, the temperature rose to 104.6 F., the pulse rate to 160 and the respiratory rate to 50. He recovered from this acute episode within a few days, but the discharge from the wound continued unabated. A phrenicectomy was performed on August 12. However, when he left the hospital, the wound was discharging a large amount of pus. Follow-up disclosed that the patient died at Sea View Hospital on Jan. 16, 1928.

#### SUMMARY

Assessing the results attained with thoracoplastic operations in pulmonary tuberculosis, one must not lose sight of the fact that patients with chronic tuberculous cavities are not necessarily doomed to absolute and immediate invalidism. A glance into the wards or into the waiting room in any follow-up clinic of a hospital for patients with advanced tuberculosis will dissipate this notion. Practice in large cities often brings one into contact with persons who have pursued arduous occupations for years despite cavities in the lungs and sputum containing demonstrable tubercle bacilli. Some of these patients, sick since their twenties, reach 40, 50, 60 or more years before they succumb to an acute exacerbation, some complication or an entirely independent condition. Among the patients in outdoor clinics, one finds a fairly large number who actively pursue their lifework despite quiescent cavity lesions. As a rule, the fact that a person is considered a sufficiently good operative risk to be submitted to surgical treatment is in itself an indication of a high degree of chronicity of the tuberculous process in the lungs. One with an acutely or subacutely progressive lesion is, almost without exception, not chosen for operation. And patients with intensely chronic tuberculous lesions are apt to live for many years and be long able to pursue their occupation under conservative treatment.



We also feel it necessary to touch in cursory fashion on a point which we intend to amplify in a subsequent communication. It is not our intention in this paper to compare our results with those reported by others, especially in the surgical literature. It is essential to bear in mind that if a tuberculous patient suffers from few or no symptoms of the disease, especially if he is free from symptoms due to tuberculous toxemia before the operation, his subsequent well-being is not necessarily to be attributed to the operation. This class of tuberculous patients bear any surgical operation quite well. We realize that this is a platitude, but it is a platitude the neglect of which has furnished the basis for many of the results reported in the recent literature on the surgical treatment of tuberculosis. It cannot be too strongly emphasized that the presence of anatomic changes in the lungs, no matter how extensive, does not call for treatment in the absence of toxic symptoms. The history of phthisiotherapy is replete with therapeutic measures which gained temporary repute through their application in cases of purely "anatomic" tuberculosis.

Bearing these points in mind, we are in a position to evaluate the benefits derived by the forty-four patients whose histories we have detailed. The fact is worthy of reiterated emphasis that we have included only those patients who have been kept under continuous observation in the sanatorium, hospital and finally in the outdoor clinic for from two to ten years. Our results are as follows:

1. The postoperative mortality, death within one week, was four out of forty-four, or 9 per cent. Fourteen out of forty-four, or 30 per cent, died within one year after the operation. This proportion is higher than would be expected under any other form of treatment, or no treatment at all, in patients with the variety of pathologic changes in the lungs and the paucity of toxic symptoms necessary to render them good operative risks.

2. We also find that of the forty-four patients operated on, seven, or 15.9 per cent, are still in the hospital, and fourteen, or 31.8 per cent, are still under treatment in the outdoor clinic or some other institution, and are unable to do any work whatever, suffering as they do from chronic and active pulmonary tuberculosis. In other words, irrespective of the local results attained by the operation or of its influence on the symptoms of the disease, 48 per cent of the surviving patients have not been rehabilitated to such a degree as to fit them to reengage in their occupations or to do any work whatever. In this class should be included those who died within a year of the operation. If this is done, it is found that in 80 per cent of the cases (thirty-four of forty-four), no benefit has been derived from the thoracoplastic operation.

3. Five patients are fit for some work. However, each suffers from symptoms of pulmonary tuberculosis. Each one expectorates more or less profusely, is dyspneic and fatigued by slight muscular exertion (cases 1, 2 and 3). One (case 4) has been in various sanatoriums for eight years since the operation. Some patients (e. g., case 7) might have been considered "cured" if the results had been reported prematurely.

4. In the cases in which thoracoplasty was performed with a view to controlling recurrent pulmonary hemorrhage, even though the general condition may have been fair or good (cases 27, 29, 30, 31 and 33), the results have not been encouraging. The patients still bleed. Indeed, some patients, in whom hemorrhage was not the symptom which induced surgical intervention, or who never bled, began to bleed more or less copiously after the operation (cases 1, 5, 18 and 19).

5. In no case have we observed that a tuberculous cavity was completely collapsed after thoracoplastic operation. Unequivocal proof of this fundamental point has been afforded by our examination of serial roentgen pictures of every patient operated on. Moreover, examination of the lungs of those coming to necropsy showed that the cavities remained quite large and open (cases 15, 18, 20, 22 and 24). Our roentgenologic and postmortem experience teaches that collapse of tuberculous cavities by thoracoplastic operation, which is supposed to promote their obliteration, is entirely illusory.

6. Of the ten patients with pyopneumothorax submitted to thoracoplastic operations, four are dead, two are still in the hospital very ill, three attend the follow-up clinic with annoying draining sinuses, and one, though still having a draining sinus, is well enough to do part time work (case 36).

7. It is our impression that had we cared for these forty-four patients along tried and conservative lines of treatment or had we allowed them to drift without treatment, the final results would have been much better. The number that died during the period these patients were under observation would surely have been smaller; the number fit for the kind of work pursued by the five patients considered rehabilitated would have been much larger.

8. We have not observed a patient who, when seen several years after a thoracoplastic operation, was free from symptoms of tuberculous disease to the same extent as we often observe following the application of climatic or institutional treatment, with or without artificial pneumothorax.

# IRON IN HUMAN BLOOD

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The recent enlightening researches on iron metabolism have given increased emphasis to the importance of iron in the blood stream. There are four interesting phases in which blood iron participates: (1) storage, (2) catalysis, (3) ferrification and (4) production of hemoglobin.

## ACTIVITIES OF BLOOD IRON

*Storage.*—The factors determining the storage of iron in the body are indefinite, although in children it has been suggested that a higher intake of iron results in increased storage.<sup>1</sup> In any event, the circulation figures prominently in this activity by transporting and distributing the iron stored in the body. However, the form in which iron is transported in the blood stream is vague. Free iron is known to be highly toxic in the blood stream. Its great affinity for nitrogenous complexes<sup>2</sup> facilitates the assumption that iron occurs in some such union. One plausible explanation of the iron traffic designates the red blood cell as the carrier, the lecithin of the corpuscular envelop binding the iron loosely.<sup>3</sup> The storage of iron in any cell or tissue would then depend on its possession of iron-avid substances which could displace the lecithin in a more stable combination with iron. The spleen would ultimately receive the remaining iron on completion of the life cycle of the erythrocyte in that organ. In addition to the spleen, the other great storehouses are the liver and the blood hemoglobin. These reservoirs maintain a total sum of iron which is constant. Although the propor-

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tion stored in each is always shifting, a loss in the iron content of any one is reflected in an associated gain in the others.<sup>4</sup>

*Catalysis.*—Warburg's<sup>5</sup> establishment of the respiratory ferment as an iron complex has been a stimulus to the study of metallic catalysts and enzymes. The chromatin in the nucleus of every cell contains concealed iron.<sup>6</sup> That the nuclear material dominates the metabolism of the cell is also a fact. The ferruginous portion of hemoglobin, the heme, has recently been shown to be closely related to enzymes and to various undetermined substances in animal cells.<sup>7</sup> This relationship demands attention because of its bearing on the transformation and interchange of iron in the organism.

*Ferrification.*—Ferrification, to introduce a new term for the deposition of iron in inflammatory areas, is a protective process similar in purpose to calcification. The migration of the red blood cells into inflammatory areas has not been greatly emphasized hitherto because of the massiveness of the concomitant leukocytosis, which has overshadowed the important part played by iron in the classic picture of inflammation. The mobilization and deposition of iron in areas of inflammation have been satisfactorily demonstrated by Menkin.<sup>8</sup> More recently he has advanced a definite protective function for iron in tuberculous lesions.<sup>9</sup> The fact that iron also accelerates the growth of connective tissue cells<sup>9</sup> suggests that this element may be influential in walling off pathologic processes and in instituting the repair of tissue. The excess deposits of iron which are known to occur in hemochromatosis and hepatic cirrhosis are also accompanied by great fibrous overgrowth.<sup>10</sup> Cancer cells are reported particularly rich in iron.<sup>3</sup> Aside from the obvious increase of iron in the excessive chromatin material which is found, the exact status of the metal in neoplasms is less evident.

*Production of Hemoglobin.*—The great importance attached to iron in the various activities described is not reflected quantitatively in the

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blood stream. Almost all of the iron found is part of the hemoglobin molecule. Nevertheless, the earlier experimenters described a non-hemoglobinous portion of iron as a substantial fraction of the whole blood iron.<sup>11</sup> The existence of nonhemoglobinous iron in comparatively large quantities, however, is open to doubt. In the first place, the earlier workers determined iron by methods which are now considered inaccurate. In the second place, they calculated the iron content of hemoglobin erroneously by using an incorrect factor. They were not aware of the Butterfield<sup>12</sup> factor—iron equals 0.335 per cent of hemoglobin—which is accepted today. In the third place, they estimated the hemoglobin content by direct colorimetry, a procedure still utilized in modern clinical methods, although far from yielding accurate results because of the presence in the blood of interfering extraneous pigments, such as bilirubin, carotene and carboxyhemoglobin.

#### EXPERIMENTAL MATERIAL

To our knowledge no extensive report of whole blood iron is available. We therefore considered the desirability of determining by an accurate method whole blood iron in a large series of normal male and female subjects. We experimented on 100 medical students in the freshman and sophomore years, varying in age from 20 to 25 years, and 50 nurses, varying in age from 20 to 30 years.

#### METHODS

In each case blood was drawn in a preabsorptive period, from the men at 12 noon just before lunch, and from the women at 9 a. m. before breakfast, during the months from January to April, inclusive. We specify the time as Rabinovitch<sup>13</sup> showed that the hemoglobin content varies somewhat at different periods of the day, and Lippincott<sup>14</sup> found that hemoglobin exhibits a monthly or a seasonal variation.

Determinations of iron were made on oxalated blood. The method employed was that of Wong<sup>15</sup> except for some slight modifications. To 0.5 cc. of blood accurately pipetted into a 50 cc. volumetric flask was added 2.5 cc. of concentrated sulphuric acid, and the flask was revolved rapidly. Two cubic centimeters of a saturated solution of potassium persulphate previously measured into small tubes was then added by means of the original blood pipet (assuring rinsing) to oxidize the iron to the ferric state. About 25 cc. of distilled water was added

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12. Butterfield, E. E.: Ueber die Lichtextinktion, das Gasbindungsvermögen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und krankhaften Zuständen, *Ztschr. f. physiol. Chem.* **62**:173, 1909.

13. Rabinovitch, I. M.: Variations of the Percentage of Hemoglobin in Man During the Day, *J. Lab. & Clin. Med.* **9**:120, 1923.

14. Lippincott, L. S.: Hemoglobin and Erythrocytes in the South, *J. Lab. & Clin. Med.* **12**:679 (April) 1927.

15. Wong, S. Y.: Colorimetric Determination of Iron and Hemoglobin in Blood, *J. Biol. Chem.* **77**:409 (May) 1928.

only after the flask had been cooled under the tap. The proteins were then precipitated by the addition of 2 cc. of a 10 per cent solution of sodium tungstate. The flask was made up to mark with distilled water, and the contents were thoroughly mixed by shaking. As much of the clear supernatant liquid as possible was filtered through acid-washed paper into a cylinder, in which exactly 20 cc. was collected.

To 1 cc. of a standard iron solution containing 0.1 mg. of iron, 1 cc. of concentrated sulphuric acid and 0.8 cc. of a saturated solution of persulphate were added, and the cylinder was filled to the 20 cc. mark with distilled water. Both the standard and the unknown solution then received 1 cc. of saturated potassium persulphate and 4 cc. of third-normal potassium thiocyanate. The cylinders were stoppered and shaken, and samples from each were compared in a colorimeter.

The ubiquitous nature of iron makes for ease of contamination. Error is overcome by scrupulous care of the reagents. The water and sulphuric acid used should be redistilled from a glass apparatus, and the chemicals and filter paper employed should be frequently tested for iron. Fading of the ferric thiocyanate color produced is negligible when speedy comparisons are made.

Blood counts were made with standardized pipets and standardized counting chambers.

For the determinations of hemoglobin, an older model of the Dare hemoglobinometer using candle light was employed for the samples of blood in table 1, and a newer model utilizing electric light for the samples of blood in tables 2 and 3. These determinations, as well as the blood counts, were made on samples of blood obtained by cutaneous puncture of the lobe of the ear.

#### EXPERIMENTAL DATA

The figures for white and red cells and for iron hemoglobin, iron index and iron color index are given in tables 1, 2, 3 and 4.

*Blood Iron.*—Most figures for blood iron are at least thirty years old. They were obtained by methods no longer in use. Fowell<sup>1</sup> quoted eight authors whose figures ranged from 44 to 57 mg. per hundred cubic centimeters of blood. Some recent figures which have been published are given in table 5.

The figures of Murphy, Lynch and Howard,<sup>16</sup> in comparison with those of others, are too low, a fact which they themselves stated.

Our figures indicate that in men the whole blood iron ranges from 40.05 to 58.60 mg., with an average of 50.01 mg. per hundred cubic centimeters and a probable error<sup>17</sup> of 2.56. The figures for women are lower, showing a range from 33.45 to 49.25 mg., with an average of 42.67 mg., per hundred cubic centimeters and a probable error of 2.13.

*Hemoglobin.*—For converting the value of whole blood iron to grams of hemoglobin, we employed Butterfield's factor, iron equals 0.335 per cent of hemoglobin.

16. Murphy, W. P.; Lynch, R., and Howard, I. M.: Value of Determinations of Iron Content of Whole Blood, *Arch. Int. Med.* **47**:883 (June) 1931.

17. The probable error of distribution. Thus, any normal whole blood iron stands a chance of falling somewhere within the range between average plus probable error and average minus probable error.

TABLE 1.—*Normal Whole Blood Iron; Determinations of Iron on Blood from 50 Normal Male Students\* (Wong's Method)*

Name	Red Blood Cells	White Blood Cells	Mg. of Iron in 100 Cc. of Blood	Percentage of Hemo- globin, Dare Method†	Hemo- globin,‡ Gm. in 100 Cc. of Blood	Iron Index§	Iron Color Index#
Rocc.	5,184,000	9,200	55.00	88	16.42	10.61	1.06
Roch.	4,864,000	8,000	47.75	88	14.25	9.83	0.98
Have.	5,322,000	5,800	50.90	89	15.79	9.56	0.96
Kazl.	5,280,000	9,000	55.85	93	16.67	10.58	1.06
Ture.	4,768,000	7,400	40.05	85	11.95	8.37	0.84
Dana.	5,664,000	6,200	57.00	87	17.01	10.02	1.00
Dwye.	5,344,000	9,800	55.25	91	16.49	10.35	1.04
Hill.	4,892,000	9,200	50.87	85	15.18	10.40	1.04
Flyn.	5,216,000	9,600	50.05	86	14.92	9.59	0.96
Dete.	5,024,000	9,000	53.05	82	15.84	10.55	1.06
King.	4,896,000	7,800	47.85	93	14.28	9.76	0.98
Deet.	5,376,000	5,800	49.25	86	14.70	9.16	0.92
Stro.	5,344,000	8,400	52.90	90	15.79	9.89	0.99
Ster.	5,152,000	7,800	49.10	92	14.66	9.53	0.95
Roon.	5,056,000	7,000	46.70	85	13.94	9.23	0.92
Tabo.	4,706,000	7,200	49.00	88	14.63	10.41	1.04
Rane.	5,408,000	9,600	53.10	88	15.85	9.82	0.98
Spra.	4,992,000	9,600	45.50	90	13.58	9.12	0.91
Kuzi.	5,066,000	5,000	46.95	83	14.01	9.28	0.93
Seam.	5,618,000	5,200	50.75	87	15.15	9.03	0.90
Tana.	4,388,000	9,200	46.22	85	13.80	10.83	1.08
Klei.	4,548,000	8,000	55.85	83	16.66	12.28	1.23
Kech.	4,896,000	5,400	50.50	86	15.01	10.32	1.03
Shau.	4,992,000	9,200	53.32	88	15.91	10.69	1.07
Jago.	4,832,000	8,000	53.45	89	16.95	11.06	1.11
Burn.	4,704,000	7,000	54.65	90	16.30	11.61	1.16
SteI.	5,152,000	6,600	44.25	90	13.27	8.59	0.86
Kay.	5,056,000	9,600	54.05	85	16.12	10.69	1.07
Byrn.	4,800,000	7,800	56.50	85	16.87	11.77	1.18
Camp.	5,088,000	9,400	44.45	89	13.25	8.75	0.88
Mest.	4,640,000	10,400	50.00	87	14.86	10.77	1.08
O'Sul.	5,120,000	9,600	54.05	86	16.12	10.55	1.06
O'Bri.	4,352,000	7,800	54.05	86	16.12	12.42	1.24
Proc.	4,608,000	6,400	54.95	83	16.40	11.92	1.19
Pani.	4,288,000	6,400	51.30	85	15.31	11.96	1.20
Fior.	4,992,000	5,600	55.80	84	16.66	11.18	1.12
Finn.	5,056,000	8,200	54.65	86	16.31	10.81	1.08
Gree.	4,768,000	8,800	51.30	82	15.31	10.76	1.08
Fras.	4,864,000	8,400	51.80	82	15.46	10.65	1.07
Form.	4,896,000	6,400	56.80	89	16.95	11.60	1.16
Lafk.	5,024,000	5,800	50.75	89	15.13	10.09	1.01
Lark.	5,152,000	7,000	55.25	85	16.49	10.72	1.07
Lang.	4,832,000	5,400	47.30	86	14.12	9.79	0.98
Iver.	5,056,000	8,600	44.45	83	13.25	8.79	0.88
Homa.	5,120,000	8,600	53.75	85	16.03	10.49	1.05
Hohl.	4,576,000	11,000	47.70	86	14.24	10.42	1.04
John.	4,768,000	4,400	55.00	89	16.42	11.53	1.15
Ferl.	4,960,000	5,600	48.80	90	14.57	9.83	0.98
Durr.	4,544,000	7,600	47.30	87	14.12	10.41	1.04
Appe.	4,832,000	5,600	47.60	85	14.21	9.85	0.99
Average	4,963,520	7,680	51.05	87	15.25	10.32	1.03

\* The students were from 20 to 25 years of age.

† The percentage of hemoglobin was determined with the old Dare hemoglobinometer.

‡ The number of grams of hemoglobin was estimated from the blood iron. Hemoglobin contains 0.335 per cent of iron (Butterfield).

$$\frac{\text{Mg. of iron in 100 cc. of blood}}{3.35} = \frac{49.75}{3.35} = 14.8 \text{ Gm. of hemoglobin.}$$

§ The iron index was determined by the Murphy method:

$$\frac{\text{Mg. of iron in 100 cc. of blood}}{\text{Red blood cells in millions}} = \frac{55.00}{5.18} = 10.61.$$

# The iron color index was determined by the following ratio:  $\frac{\text{Percentage of iron}}{\text{Per Cent of Red Blood Cells}}$

(50 mg. of iron in 100 cc. of blood equals 100 per cent of iron; 5,000,000 red blood cells equal 100 per cent of red blood cells).

TABLE 2.—*Normal Whole Blood Iron; Determinations of Iron on Blood from 50 Normal Male Students\* (Wong's Method)*

Name	Red Blood Cells	White Blood Cells	Mg. of Iron in 100 Cc. of Blood	Percent- age of Hemo- globin, Dare Method†	Gm. of Hemo- globin in 100 Cc. of Blood, Dare Method†	Hemo- globin, Gm. in 100 Cc. of Blood	Iron Index	Iron Color Index
Sell.....	4,864,000	5,000	49.75	96	15.2	14.85	10.22	1.02
Kenn.....	5,068,000	5,600	48.55	104	16.4	14.48	9.59	0.96
Scan.....	5,280,000	4,800	50.50	93	14.8	15.07	9.56	0.96
Koch.....	4,544,000	7,600	46.50	103	16.5	13.88	10.23	1.02
Lorh.....	5,408,000	9,800	50.00	97	15.4	14.92	9.43	0.94
Mart.....	5,312,000	8,600	54.45	95	15.2	16.25	10.23	1.02
Donn.....	5,312,000	6,600	49.12	97	15.5	14.66	9.24	0.92
Down.....	5,088,000	9,800	43.85	95	15.0	13.09	8.62	0.86
Hugh.....	5,248,000	6,200	46.10	98	15.8	13.76	8.78	0.88
Bell.....	5,376,000	9,400	46.10	105	16.8	13.76	8.57	0.86
Bill.....	5,024,000	6,800	47.15	108	17.2	14.07	9.38	0.94
McDe.....	5,216,000	8,400	47.15	108	17.2	14.07	9.04	0.90
Comp.....	5,180,000	8,200	47.30	106	16.9	14.12	9.13	0.91
Coll.....	4,416,000	4,400	48.30	100	16.4	14.42	10.94	1.09
Dugg.....	5,216,000	6,000	49.12	105	16.8	14.66	9.42	0.94
Blen.....	4,320,000	7,200	42.90	98	15.6	12.81	9.93	0.99
Hart.....	5,162,000	9,600	50.05	97	15.4	14.94	9.69	0.97
Hart.....	4,512,000	5,000	51.30	95	15.0	15.31	11.37	1.14
Mc'te.....	4,896,000	10,000	47.15	92	14.6	14.07	9.63	0.96
Forr.....	4,608,000	8,200	45.65	97	15.4	13.63	9.91	0.99
Kova.....	4,766,000	7,800	53.20	96	15.2	15.88	11.19	1.12
Roml.....	5,376,000	5,800	42.25	97	15.4	12.61	7.85	0.78
Munc.....	5,024,000	6,400	48.55	92	14.6	14.48	9.66	0.97
New.....	4,832,000	5,600	46.30	95	15.2	13.82	9.58	0.96
Duff.....	4,960,000	8,800	47.60	97	15.4	14.21	9.59	0.96
Rous.....	4,896,000	9,600	50.05	98	15.6	14.94	10.20	1.02
Maus.....	4,864,000	6,700	47.85	96	15.2	14.28	9.84	0.98
Wall.....	5,184,000	9,000	42.75	95	15.2	12.76	8.24	0.82
Roe.....	5,056,000	8,600	47.60	98	15.6	14.21	9.41	0.94
Riem.....	5,344,000	9,200	54.35	94	15.0	16.22	10.17	1.02
McDo.....	5,376,000	7,800	46.30	97	15.4	13.82	8.61	0.86
Coop.....	5,344,000	8,000	46.10	99	15.8	13.76	8.63	0.86
Paol.....	5,216,000	5,600	49.75	96	15.2	14.85	9.54	0.96
Henr.....	5,088,000	8,200	56.50	98	15.6	16.88	11.10	1.11
Ever.....	5,248,000	6,800	58.60	96	15.4	17.49	11.14	1.11
Evan.....	5,472,000	9,800	47.85	97	15.4	14.28	8.74	0.87
Kell.....	5,120,000	10,800	52.10	95	15.2	15.55	10.17	1.02
Dwar.....	4,864,000	9,400	48.05	98	15.6	14.34	9.88	0.99
Eaga.....	5,248,000	7,000	48.80	97	15.4	14.54	9.29	0.93
Dorw.....	5,120,000	6,800	52.10	93	14.8	15.55	10.17	1.02
Mugg.....	4,960,000	9,000	51.30	95	15.2	15.31	10.34	1.03
Glen.....	5,056,000	8,200	54.05	97	15.4	16.13	10.69	1.07
Bens.....	5,088,000	9,000	52.35	98	15.6	15.63	10.03	1.00
Nagl.....	4,864,000	5,400	50.00	95	15.2	14.92	10.28	1.03
Camp.....	5,152,000	5,600	49.80	97	15.4	14.86	9.67	0.97
Smyr.....	4,960,000	6,200	50.75	98	15.6	15.15	10.23	1.02
Rose.....	5,058,000	7,600	48.55	94	15.0	14.48	9.42	0.94
Nelg.....	4,640,000	4,800	52.35	97	15.4	15.63	11.28	1.13
Dash.....	5,152,000	5,200	46.45	95	15.2	13.87	9.02	0.90
Bern.....	4,892,000	6,000	45.45	96	15.4	13.55	9.29	0.93
Average.....	5,045,280	7,438	48.97	97.5	15.5	14.62	9.71	0.97

\* The subjects were from 20 to 25 years of age.

† The percentage and grams of hemoglobin were determined with the new Dare hemoglob-  
inometer.



TABLE 3.—*Normal Whole Blood Iron; Determinations of Iron on Blood from 50 Normal Female Subjects\* (Wong's Method)*

Name	Red Blood Cells	White Blood Cells	Mg. of Iron in 100 Cc. of Blood	Percent- age of Hemo- globin, of Dare Method†	Gm. of Hemo- globin, in 100 Cc. of Dare Method†	Hemo- globin, Gm. in 100 Cc. of Blood	Iron Index	Iron Color Index
Have.....	4,352,000	8,600	43.85	96	15.2	13.09	10.01	1.06
Pole.....	4,736,000	6,600	46.10	94	15.0	13.76	9.73	1.03
Ande.....	4,288,000	5,800	37.30	88	14.0	11.13	8.69	0.92
Herv.....	4,640,000	10,600	46.30	94	15.0	13.82	9.93	1.03
Clar.....	4,096,000	8,600	37.05	95	15.2	11.06	9.04	1.96
Dahl.....	4,480,000	8,800	41.15	93	14.8	12.28	9.18	0.96
Byer.....	4,736,000	8,000	39.50	90	14.4	11.79	8.34	0.88
Detl.....	4,576,000	6,000	39.35	96	15.2	11.74	8.59	0.91
Brow.....	4,480,000	5,000	33.45	97	15.4	9.98	7.46	0.78
Myer.....	4,352,000	5,400	43.65	93	14.8	13.03	10.03	1.05
Kuce.....	4,640,000	6,000	41.65	94	15.0	12.43	8.95	0.95
Dewe.....	4,512,000	6,200	43.45	93	14.8	12.97	9.63	1.02
Deer.....	4,576,000	7,200	42.90	95	15.2	12.81	9.37	0.99
Lisc.....	4,480,000	7,000	42.75	92	14.8	12.76	9.54	0.99
Moom.....	4,576,000	5,800	42.90	93	14.8	12.81	9.37	0.99
Cope.....	4,832,000	7,000	46.95	96	15.2	14.01	9.71	1.03
Trei.....	4,256,000	5,400	40.65	90	14.4	12.13	9.54	0.99
Schl.....	4,352,000	6,000	41.00	91	14.5	12.24	9.42	0.99
Kota.....	4,896,000	7,400	38.15	96	15.4	11.89	7.79	0.82
Stre.....	4,448,000	5,400	42.75	97	15.4	12.76	9.61	0.99
Nels.....	4,384,000	6,200	42.90	93	14.8	12.80	9.78	1.03
Akin.....	4,224,000	8,000	47.85	90	14.4	14.27	11.33	1.19
Lewi.....	4,640,000	5,600	46.10	92	14.8	13.76	9.93	1.05
Glas.....	4,672,000	9,600	43.45	97	15.4	13.57	9.73	0.99
Yost.....	4,320,000	6,800	40.00	94	15.0	11.94	9.26	0.98
Carb.....	4,128,000	7,000	38.60	88	14.0	11.52	9.35	0.98
McDo.....	4,544,000	4,400	44.05	95	15.1	13.15	9.69	1.02
Romp.....	4,640,000	7,600	45.45	94	15.0	13.57	9.79	1.03
Dier.....	4,160,000	5,800	41.50	90	14.2	12.39	9.97	1.05
Wese.....	4,768,000	5,600	40.30	96	15.3	12.03	8.45	0.89
Mete.....	4,074,000	10,000	39.85	90	14.3	11.89	9.78	0.99
Swar.....	4,544,000	6,000	40.10	93	14.8	11.97	8.82	0.93
Mors.....	4,768,000	4,600	41.30	94	15.0	12.33	8.66	1.02
Drap.....	4,448,000	7,600	37.30	94	15.0	11.13	8.38	0.88
Schl.....	4,576,000	9,600	44.65	92	14.7	13.13	9.76	1.02
Will.....	4,192,000	5,800	46.30	92	14.7	13.82	11.04	1.16
Full.....	4,480,000	7,000	41.15	95	15.0	12.28	9.18	0.97
Olms.....	4,512,000	8,800	44.65	93	14.8	13.33	9.89	1.05
Vejy.....	4,416,000	5,400	46.10	91	14.5	13.76	10.44	1.10
Pena.....	4,064,000	7,000	44.05	89	14.4	13.15	10.83	1.14
Schm.....	4,288,000	5,800	40.25	88	14.1	14.70	11.48	1.26
Boyd.....	4,122,000	5,800	44.45	89	14.3	13.27	10.78	1.12
Schm.....	4,384,000	7,200	46.10	87	14.0	13.76	10.51	1.11
Fish.....	4,800,000	6,400	45.45	95	15.2	13.57	9.47	0.99
McAl.....	4,384,000	7,800	46.10	92	14.7	13.76	10.51	1.11
Wals.....	4,416,000	6,000	40.30	94	15.0	12.03	9.13	0.96
O'Nei.....	4,160,000	4,600	42.55	90	14.4	12.69	10.23	1.08
Phil.....	4,384,000	5,000	40.50	90	14.4	12.09	9.24	0.98
Tome.....	4,768,000	5,800	44.25	96	14.3	13.21	9.26	0.98
McKe.....	4,320,000	7,600	45.85	88	14.1	13.68	10.61	1.12
Average.....	4,457,000	6,796	42.67	92.5	14.8	12.74	9.59	1.01

\* The subjects varied from 20 to 30 years of age.

† The percentage and grams of hemoglobin were determined with the new Dare hemoglobinometer.

Comparisons of the whole blood method with the accepted oxygen capacity method for the estimation of hemoglobin show close agreement, thus confirming the equality of hemoglobinous iron with whole blood iron.<sup>18</sup> The transport iron which is constantly being carried by the blood to and from the various storehouses, for the bone marrow, for

TABLE 4.—*Normal Whole Blood Iron, Averages, Determinations of Blood on 100 Normal Male Students and 50 Normal Women*

Group	Red Blood Cells	White Blood Cells	Mg. of Iron in 100 Cc. of Blood	Percent- age of Hemo- globin, Dare Method*	Gm. of Hemo- globin in 100 Cc. of Blood, Dare Method	Hemo- globin, Gm. in 100 Cc. of Blood†	Iron Index	Iron Color Index
Table 1, 50 male students.....	4,963,520	7,680	51.05	87	....	15.25	10.32	1.03
Table 2, 50 male students.....	5,045,280	7,438	48.97	97.5	15.5	14.62	9.71	0.97
Average of tables 1 and 2, 100 male students.....	5,004,400	7,559	50.01	....	....	14.93	10.01	1.00
Table 3, average, 50 women.....	4,457,680	6,796	42.67	92.5	14.8	12.74	9.59	1.01

\* Different models of the Dare hemoglobinometer were used for tables 1 and 2.

† The hemoglobin was estimated from whole blood iron (iron equals 0.335 per cent of hemoglobin).

TABLE 5.—*Recent Figures for Blood Iron*

Author	Mg. of Iron per 100 Cc. of Blood			
	In Men	Number of Samples	In Women	Number of Samples
Berman (J. Biol. Chem. <b>35</b> : 231, 1918).....	46.60	6	.....	..
Sackett (J. Lab. & Clin. Med. <b>10</b> : 1018, 1925).....	56.02	15	51.20	14
Murphy, Lynch and Howard, <sup>16</sup> 1931.....	44.84	18	42.48	21

catalysis and for other processes, occurs in only minute quantities at any one time. Over a given period it may be responsible for a large store of iron. But in any one sample of blood almost the entire amount of iron is bound by the hemoglobin molecule. Consequently, accurate estimation of the hemoglobin is possible from figures for whole blood iron.

Recently serum iron has received a great deal of attention. Determinations of iron in blood serum in this laboratory (unpublished results), as well as those reported by others,<sup>19</sup> rule out the quantitative

18. Lindsay, J. W.; Rice, E. C., and Selinger, M. A.: Plea for Standardized Method of Estimating and Reporting Hemoglobin Values, J. Lab. & Clin. Med. **11**:737 (May) 1926. Karshan, M., and Freeman, R. G., Jr.: Study of Hemoglobin Methods, *ibid.* **15**:74 (Oct.) 1929.

19. Locke, A.; Main, E. R., and Rosbash, D. O.: Copper and Non-Hemoglobinous Iron Contents of Blood Serum in Disease, J. Clin. Investigation **11**:527 (May) 1932. Warburg, O., and Krebs, H. A.: Ueber locker gebundenes Kupfer und Eisen im Blutserum, Biochem. Ztschr. **190**:143, 1927.

significance of blood iron present in this form. In the normal male subject the serum contains approximately 0.1 mg. of iron per hundred cubic centimeters, a negligible figure representing only 0.1 per cent of the whole blood iron. Even in a condition such as pernicious anemia, in which serum iron is said to be abnormally high, it does not exceed 0.3 mg. per hundred cubic centimeters of serum. Assuming that the whole blood iron in the particular case was 15 mg. per hundred cubic centimeters (only 30 per cent of the normal), the iron present in the serum would still amount to less than 1 per cent of the whole blood iron.

In the blood of 100 normal male subjects we found a hemoglobin content varying from 11.95 to 17.49 Gm. per hundred cubic centimeters. In this series 90 per cent are included within the range of from 13 to 16.4 Gm. of hemoglobin. The average hemoglobin content was 14.93 Gm. per hundred cubic centimeters, with a probable error of 0.76. Wintrobe<sup>20</sup> reported an average hemoglobin content of 14.53 Gm. per hundred cubic centimeters for 100 men. His figures were obtained by the Newcomber method after standardization of the instrument by the oxygen capacity method. He also stated that 274 determinations made in different parts of the world indicate a hemoglobin content of 14.61 Gm. per hundred cubic centimeters of blood. This figure agrees closely with that of Osgood, who reported 14.66 Gm. on the basis of a red cell count of 5,000,000.<sup>21</sup>

Our findings indicate that the average hemoglobin content for women is 12.74 Gm. per hundred cubic centimeters of whole blood, with a probable error of 0.66. Variations range from 9.98 to 14.70 Gm.

The figures for hemoglobin obtained with the new Dare hemoglobinometer given in tables 2 and 3 show little relationship to those accurately derived from the whole blood iron. This lack of agreement emphasizes the error possible with similar clinical instruments, which at best may serve to reflect but roughly the true blood picture. Extraneous blood pigments, such as bile pigments and carotene, play no little part in interfering with the accuracy of most of the clinical colorimetric methods now in use.

*Iron Index.*—This iron index, which was introduced by Murphy, Lynch and Howard, established a relationship between the individual red cell and its iron content.<sup>16</sup>

$$\frac{\text{Mg. of iron in 100 cc. of whole blood}}{\text{First three figures of the red cell count}} = \text{iron index.}$$

Hemoglobin, according to the Butterfield factor used, is a multiple of the iron in the blood stream. Consequently, to record the relative

20. Wintrobe, M. M.: Hemoglobin Standards in Normal Men, *Proc. Soc. Exper. Biol. & Med.* **26**:848 (June) 1929.

21. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards, *Arch. Int. Med.* **37**:685 (May) 1926.

amount of iron in the red cell by the iron index is merely another way of designating the amount of hemoglobin contained in each red cell. In searching for precisely such an index which would express the hemoglobin content per red cell, the older hematologists formulated the color index. The reliability of the color index depends on the accuracy of the figures in the ratio  $\frac{\text{percentage of hemoglobin}}{\text{percentage of red blood cells}}$ , from which it is derived. Since the whole blood iron can be determined more accurately than the percentage of hemoglobin (estimated by any of the ordinary clinical instruments), the iron index has the advantage of greater accuracy over the older color index.

Murphy, Lynch and Howard reported that the average iron index for normal men and women falls between 8 and 9.<sup>16</sup> Clinically, they substituted the iron index for the color index in differentiating pernicious anemia from secondary anemia. Thus an iron index above 10 corresponds to a color index of +1, which is characteristic of pernicious anemia. An iron index below 8 corresponds to a color index of -1, which is characteristic of secondary anemia.

Our results indicate that the iron index for normal men is 10.01, with a probable error of 0.65, and for normal women, 9.59, with a probable error of 0.56. The low figures for whole blood iron of Murphy and his associates are responsible for the correspondingly low iron indexes which they obtained. Our figures for the iron index establish a new range from 9 to 11 for the average normal man or woman. The normal variations given in tables 1, 2 and 3 are, however, too great in our series to permit a sharp demarcation of the pathologic index from the normal index. As a result, the iron index suffers in its clinical application.

*Iron Color Index.*—In order to retain the convenient +1 and -1 of the older color index and yet take advantage of the greater accuracy of the iron index, we propose for clinical use the iron color index. The older color index, which we designate as the hemoglobin color index, is derived from the ratio  $\frac{\text{percentage of red blood cells}}{\text{percentage of hemoglobin}}$ . The new color index, which we designate as the iron color index, is derived from the ratio  $\frac{\text{percentage of iron}}{\text{percentage of red blood cells}}$ .

In order to determine the percentage of iron, we took our averages of 50 mg. of iron per hundred cubic centimeters of blood in the men and 42.7 mg. of iron per hundred cubic centimeters of blood in the women as representing 100 per cent. Thus, blood from a man which contains 40 mg. of iron per hundred cubic centimeters is regarded as having 80 per cent of the normal iron content.

The iron color index, which runs parallel in value to the old hemoglobin color index, may be used to advantage clinically if certain principles are kept in mind. Thus, the iron color index is applicable only to

TABLE 6.—Miscellaneous Patients; Whole Blood Iron (Wong's Method)

Name	Diagnosis	Red Blood Cells	White Blood Cells	Mg. of Iron in 100 Cc. of Blood	Percent- age of Hemo- globin, Dare Method*	Hemo- Gm. in 100 Cc. of Blood	Iron Index	Iron Color Index
Mr. Buhl.	Carcinoma of stomach..	4,448,000	6,400	52.50	66	15.67	11.8	1.18
Mr. Bena.(1)†	Malignant condition of bone.....	3,712,000	4,600	54.05	60	16.11	14.5	1.45
Mr. Bena.(2)†	Malignant condition of bone.....	2,080,000	4,200	27.10	32	8.09	13.0	1.30
Mrs. Braw.	Carcinoma of breast....	4,256,000	4,800	27.24	75	8.13	6.4	0.67
Mrs. Geer.	Carcinoma of pelvis....	4,672,000	7,600	36.65	65	10.94	7.8	0.81
Mrs. Fole.	Carcinoma of mouth....	3,808,000	5,600	48.85	60	13.67	12.0	1.35
Mrs. Kell.	Carcinoma of pelvis....	3,904,000	4,600	46.95	62	14.01	12.0	1.26
Mr. Murp.(1)†	Carcinoma of esophagus	5,162,000	6,600	61.00	87	18.21	11.8	1.18
Mr. Murp.(2)†	Carcinoma of esophagus	4,512,000	5,400	55.30	77	16.51	12.2	1.22
Mrs. Houb.	Carcinoma of pelvis....	3,808,000	5,400	43.65	68	13.01	11.4	1.21
Mrs. Howa.	Carcinoma of uterus....	3,232,000	7,800	25.35	34	7.57	7.9	0.82
Mr. Garm.	Myocarditis.....	5,376,000	9,200	55.10	78	16.45	10.2	1.02
Mrs. Blot.	Hypertension.....	4,832,000	7,200	47.40	79	14.15	9.8	1.04
Mr. Whee.	Hypertension.....	4,828,000	5,600	61.70	81	18.42	12.8	1.28
Mr. Flow.	Arteriosclerosis.....	4,768,000	5,600	54.35	78	16.22	11.4	1.14
Mrs. Rose	Hypertension.....	4,576,000	8,800	48.80	79	14.57	10.6	1.12
Mrs. Kill.	Hypertension.....	4,420,000	6,200	44.85	83	13.39	10.1	1.07
Mr. Brac.	Nephritis.....	4,064,000	5,600	38.60	78	11.52	9.6	0.90
Mr. Gren.	Nephritis.....	2,080,000	60,000	14.37	20	4.29	6.9	0.69
Miss Gamm.	Nephritis.....	4,352,000	9,200	37.60	75	11.22	8.6	0.90
Mr. Cott.	Diabetes.....	4,860,000	9,000	56.10	82	16.75	11.5	1.15
Mr. Metz.(1)†	Diabetes.....	4,672,000	8,800	48.20	79	14.39	10.3	1.03
Mr. Metz.(2)†	Diabetes.....	4,330,000	9,600	49.50	83	14.78	11.4	1.14
Mrs. Brou.	Diabetes.....	5,088,000	12,800	49.25	75	14.70	9.6	1.02
Mr. Louc.	Rheumatism.....	4,896,000	5,400	53.30	85	15.91	10.9	1.09
Mrs. Frei.	Arthritis.....	4,768,000	5,400	40.60	78	12.12	8.5	0.90
Mr. Kell.	Arthritis.....	4,512,000	7,200	49.25	83	14.69	11.0	1.10
Mrs. Dreg.	Arthritis.....	4,704,000	5,400	46.30	81	13.82	9.8	0.97
Miss Cain.	Neurosis and colitis....	4,544,000	9,400	55.60	77	16.59	12.2	1.31
Miss Clrc.	Neurosis.....	4,608,000	6,600	42.35	78	12.64	9.2	0.92
Mrs. Cald.	Neurosis.....	4,540,000	6,000	40.70	78	12.15	8.9	0.94
Mr. Axen.	Neurosis.....	4,608,000	7,800	57.80	80	17.25	12.5	1.25
Mrs. Merr.	Neurasthenia.....	4,544,000	9,800	47.53	78	14.18	10.4	1.10
Mr. Lads.	Neurosis.....	4,256,000	7,200	46.40	86	13.85	10.9	1.09
Miss Gert.	Chronic appendicitis....	4,288,000	7,200	53.05	74	15.84	12.4	1.31
Mr. Burt.	Hyperacidity.....	5,056,000	6,000	46.90	79	14.00	9.3	0.93
Mr. Stew.(1)†	Mucous colitis.....	4,164,000	4,200	61.20	81	18.27	14.7	1.47
Mr. Stew.(2)†	Mucous colitis.....	4,128,000	5,000	57.50	82	17.16	13.9	1.39
Miss Hind.	Ulcerative colitis.....	3,872,000	5,800	39.20	60	11.70	10.1	1.07
Mr. Urid.	Duodenal ulcer.....	5,344,000	6,400	45.30	81	13.52	8.5	0.85
Mr. Rick.	Hyperacidity.....	4,672,000	7,800	48.50	77	14.46	10.4	1.04
Mrs. Mals.	Duodenal ulcer.....	4,576,000	9,000	50.30	77	15.01	11.0	1.16
Mrs. Dart.	Spastic colon.....	4,384,000	5,200	50.90	75	15.09	11.6	1.22
Mr. Levi.	Hyperacidity.....	5,088,000	9,400	49.12	83	14.66	9.6	0.96
Mr. Hine.(1)†	Cirrhosis of liver.....	4,064,000	5,400	48.30	75	14.42	11.9	1.19
Mr. Hine.(2)†	Cirrhosis of liver.....	4,512,000	5,800	44.45	76	13.27	9.8	0.98
Mrs. Pari.	Cholecystitis.....	4,828,000	8,800	46.50	79	13.88	9.6	1.02
Mrs. Bell.	Cholecystitis.....	4,704,000	9,000	42.75	75	12.76	9.1	0.95
Mrs. Bett.	Cholecystitis.....	4,256,000	5,000	44.45	80	13.27	10.4	1.10
Mr. Davi.	Subacute yellow atrophy of liver.....	3,168,000	5,200	42.35	48	12.64	13.3	1.33
Miss Gray.	Migraine.....	4,736,000	9,200	47.40	80	14.15	10.0	1.06
Mr. Wrig.	Petit mal epilepsy.....	4,576,000	5,600	51.10	82	15.25	11.2	1.12
Mrs. Mill.	Psychoneurosis.....	4,832,000	9,600	42.05	79	12.54	8.7	0.92
Mr. Sodo.	Fröhlich's syndrome....	5,024,000	7,400	52.90	83	15.79	10.5	1.05
Mrs. Bouk.	Incipient tuberculosis....	4,448,000	7,600	36.75	75	10.97	8.3	0.87
Mrs. Hyne.	Latent tuberculosis.....	4,862,000	6,400	50.90	80	15.19	10.4	1.10
Mr. Stro.	Acute pneumothorax....	4,960,000	9,800	48.50	82	14.48	9.8	0.98
Mrs. Hann.	Oophoritis.....	4,320,000	8,000	43.90	80	13.10	10.1	1.07
Mr. Burn.	Normal.....	5,024,000	5,400	40.90	84	12.21	8.1	0.81
Mrs. Mill.	Endocervicitis.....	4,160,000	8,400	42.65	70	12.73	10.2	1.08
Miss Bush.	Psoriasis.....	4,896,000	8,600	42.90	84	12.81	8.7	0.91
Mrs. McWi.	Lymphosarcomatosis....	3,808,000	6,200	35.45	65	10.58	9.3	0.98
Mr. Neve.	Hodgkin's disease.....	2,624,000	3,000	20.43	42	6.09	7.8	0.78
Mrs. Rice	Secondary anemia.....	2,560,000	5,000	21.93	32	6.54	8.5	0.89
Mrs. Drie.	Pernicious anemia.....	3,648,000	12,800	33.05	66	9.87	9.0	0.95
Mrs. Doyl.	Pernicious anemia.....	2,390,000	5,200	33.45	60	9.99	13.9	1.47
Mrs. Enho.	Secondary anemia.....	2,240,000	4,600	25.17	55	7.51	11.2	1.18
Mr. Voln.	Pellagra.....	4,064,000	8,000	31.80	44	9.49	7.8	0.78
Miss Lent.	Ovarian insufficiency....	4,032,000	6,800	44.25	78	13.21	11.0	1.15

\* The old model Dare hemoglobinometer was used.

† Patient with two determinations of iron.

the anemic blood picture. For normal blood, the range of the indexes recorded in tables 1, 2 and 3 is from 0.78 to 1.26; 50 per cent are  $+1$  and 50 per cent are  $-1$ . Furthermore, although the differentiation of borderline cases of hypochromic and hyperchromic anemia may be settled by the iron color index, the index is of most significance when it is a marked  $+1$  or a marked  $-1$ .

*Determinations of Blood in Pathologic Conditions.*—We have determined the red and white cell counts, iron, hemoglobin, iron index and iron color index in 63 clinical cases. The results are recorded in table 6.

#### SUMMARY

1. The average iron content of whole blood, based on analyses of samples from 100 normal men, is  $50.01 \pm 2.56$  mg. per hundred cubic centimeters. The average for 50 normal women is  $42.67 \pm 2.13$  mg. per hundred cubic centimeters. The blood of women has a definitely lower iron content than that of men.

2. Iron in whole blood is almost entirely linked with the hemoglobin molecule. Since the quantity of nonhemoglobinous iron present in the serum and the cellular elements is very small, the error in calculating hemoglobin from whole blood iron is negligible.

3. On the basis that hemoglobin contains 0.335 per cent of iron, we conclude that the average normal blood of men contains  $14.93 \pm 0.76$  Gm. of hemoglobin per hundred cubic centimeters, while the average normal blood of women contains  $12.74 \pm 0.66$  Gm. per hundred cubic centimeters.

4. By dividing the number of milligrams of iron per hundred cubic centimeters of blood by the first three figures of the red blood cell count, a quotient, which Murphy, Lynch and Howard designated as the iron index, is obtained. We have found the iron index for normal men to be  $10.01 \pm 0.65$  Gm., and for normal women,  $9.6 \pm 0.56$  Gm. of hemoglobin per hundred cubic centimeters.

5. The iron index is preferable to the color index because of the greater accuracy with which the former may be determined.

6. The iron color index, based on the ratio of the percentage of iron to the percentage of red blood cells, is also preferable to the older hemoglobin color index. The advantages to be derived from the clinical use of this index lie in its accuracy and in the retention of the convenient  $+1$  or  $-1$  designation of the older hemoglobin color index.

7. The red and white cell counts, iron, hemoglobin, iron index and iron color index in 63 clinical cases are also included in this report.

# INSENSIBLE PERSPIRATION: ITS RELATION TO BASAL METABOLISM

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The changes that occur in the body weight of normal persons from day to day or hour to hour are usually unnoticed, probably because they are relatively slight, and because attention has not been directed to such changes. It has long been recognized, however, that muscular exercise and severe work will cause a considerable loss in body weight, both through increased loss of water and through actual breakdown of the constituents of the body.

Benedict<sup>1</sup> in Boston is perhaps the foremost advocate of the clinical application of computing the metabolism by measuring the loss of weight caused by the insensible perspiration. He gives an excellent summary of the literature on this subject from the time of Sanctorius in 1614 until the present. The insensible perspiration has been defined (Benedict) as "those gaseous emanations from the body which do not appear in the form of sensible moisture or sweat, in other words, the insensible, invisible, intangible but weighable gaseous and vapor productions arising from the lungs in the process of exhalation and from the skin by due process of vaporization, i. e., excretion of moisture and CO<sub>2</sub>."

In a series of preliminary experiments Benedict found that a normal person weighing 53.5 Kg. lost an average of 27.4 Gm. per hour for thirty eight-hour periods, whereas a woman of 60 Kg. lost an average of 28.7 Gm. per hour without visible perspiration. In later experiments he obtained values of 24 Gm. per hour in a woman of 55.5 Kg. and 29 Gm. per hour in a man of 74.5 Kg.

From these observations Benedict states that the "only conclusions to be drawn from these preliminary overnight observations on normal subjects are that in general the loss is approximately proportional to the body weight, and that with extra precautions fairly uniform values on successive nights can be secured. In the earlier observations . . . it was noted that on those nights when the subjects slept very quietly the loss was much less than on nights when there was considerable restlessness."

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From the Harvard Medical School.

1. Benedict, F. G., and Root, H.: *Insensible Perspiration: Its Relation to Human Physiology and Pathology*, Arch. Int. Med. **38**:1 (July) 1926.

The possible effect of outside influences, food, etc., has also been carefully studied by Benedict. He concludes that "following the ingestion of food there is invariably an increase in the insensible loss." He also states that in overnight observations the factors seem to balance one another and give quite true values. In the present study no food was taken within at least four hours of the night weighing, and records were kept of the quality of the sleep, but no definite correlation with the insensible perspiration could be found.

The method used in the present research was exceedingly simple. The subject was weighed just before retiring and immediately on arising, accurate account being taken of the time elapsing between weighings. It is obvious that care must be taken that no hairpins, watches, etc., be removed without being accounted for, nor must the person being weighed have just taken a bath or in any way added water to the surface of the body by washing, wetting the hair, etc. Any excreta passed during the period of the weighing must be preserved and weighed. The drinking of moderate quantities of water before weighing seems to have no effect on the final overnight result.

The scales used for the weighing in the case under consideration were the so-called "silk scales," a small platform balance which is sensitive to a variation within 5 Gm. The periods of loss of weight have all been overnight ones, and the accuracy of these scales in the case of a person of normal or of average weight has been remarkable. A number of check "losses" have been made on the large Sauter balance at the New England Deaconess Hospital in Boston. The latter balance will weigh 100 Kg. on each arm with an accuracy of within 1 decigram. The check on the silk scales has been gratifying.

The present study covers a period of one hundred and sixty-six consecutive days, during which time the evening and morning weights were recorded, the duration and quality of sleep was noted, and the total and average hourly loss of moisture calculated. The basal metabolic rate was determined at approximately weekly intervals throughout the experiment, and in a few instances daily metabolism determinations were made. The entire measured loss covers a total of 1,510 hours, making this one of the longest continued series of observations on a single subject in recent years. The patient weighed 60.4 Kg. at the beginning of the experiment and 70.2 Kg. at the end of the experiment, five months later, thus closely approximating the weights of the subjects in Benedict's earlier experiments.

The normal loss per hour of body weight, as determined by Benedict and Root,<sup>1</sup> ranged from 19.5 Gm. per hour in subjects weighing 36.5 Kg. or more, through 30 Gm. per hour in subjects weighing from 60 Kg. to 67 Kg., and as high as 44 Gm. per hour in subjects weighing



90.5 Kg., thereby proving that the insensible perspiration in a normal person is in part dependent on the body surface as well as on the basal metabolic rate.

From numerous measurements made on normal persons and on patients with diabetes and diseases of the thyroid gland, Benedict and Root have compiled a table showing the predicted production of heat in calories as estimated from the insensible perspiration measured in grams lost per hour. Their table includes losses from as low as 14 Gm. per hour to as high as 58 Gm., but as the present study contains

*Twenty-Four Hour Heat Production of Human Beings Predicted from the Insensible Perspiration per Hour (Benedict and Root)*

Insensible Perspiration, Gm. per Hour	Predicted Heat, Calories per 24 Hours	Insensible Perspiration, Gm. per Hour	Predicted Heat, Calories per 24 Hours
36.....	1,590	48.....	1,965
38.....	1,655	50.....	2,025
40.....	1,715	52.....	2,085
42.....	1,775	54.....	2,145
44.....	1,840	56.....	2,210
46.....	1,900	58.....	2,275

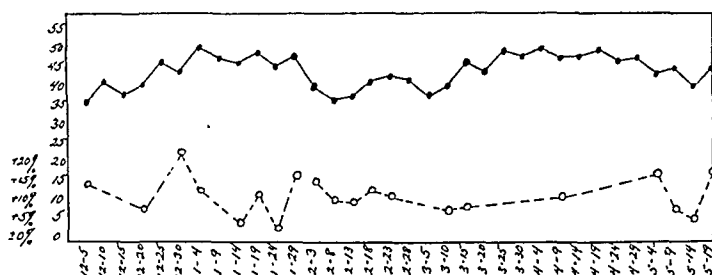


Fig. 1.—Average insensible perspiration (Gm. per hour) for five day periods, showing relationship to the basal metabolic rate for one hundred and sixty-six days.

values of over 30 Gm. per hour only, the higher values of the table will be considered here.

The normal twenty-four hour heat production of the patient under consideration in this experiment would be 1,507 calories as determined from the Benedict-Harris standard. This, on the scale presented, would correspond to an hourly loss of approximately 33 Gm. per hour. Thus, with a 10 per cent increase in the basal metabolic rate one would expect the insensible perspiration to rise to approximately 44 Gm. per hour (1,840 calories per twenty-four hours); and to 54 Gm. per hour (2,145 calories per twenty-four hours) with the basal metabolic rate 24 per cent above normal.

In figure 1 there is graphically represented the average insensible perspiration (grams per hour) and the basal metabolic rate (respiration

method) for five day periods over a total period of one hundred and sixty-six consecutive days. It will be noticed that during the first month of the experiment the insensible perspiration rose steadily, whereas the basal metabolic rate fell nearly 10 per cent near the middle of the month. On December 5, the insensible perspiration was only 36 Gm. per hour, with a measured basal metabolic rate of plus 15 per cent (1,986 calories per twenty-four hours). This, on Benedict's scale should entail a loss of 48 Gm. per hour. On December 30, the basal metabolic rate was plus 24 per cent and the insensible perspiration had risen to 45 Gm. per hour (equivalent to 54 Gm. per hour on Benedict's scale).

During January the insensible perspiration showed a still higher level over six five day periods, consistently averaging about 48 Gm. per hour, while the basal metabolic rate ranged between plus 5 per cent and plus 17 per cent. On Benedict's scale we should expect values

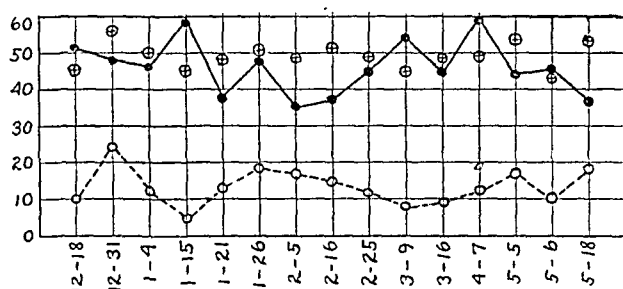


Fig. 2.—Relationship of the basal metabolic rate (white circle) to the measured insensible perspiration (black circle) and to the insensible perspiration as calculated from the Benedict-Root table (circle with cross).

of from 42 to 52 Gm. (1,775 to 2,085 calories per twenty-four hours), which was actually closely approached.

During February, both basal metabolic rate and insensible perspiration averages declined, the former averaging approximately plus 12 per cent and the latter ranging from 38 to 44 Gm. per hour. Benedict's figures for this average metabolism (plus 12 per cent or 1,986 calories per twenty-four hours) would be 48 Gm. per hour, or slightly higher than our values.

During March, the basal metabolic rate reached a low level early in the month and then began to rise slowly. The insensible perspiration rose correspondingly from 40 Gm. per hour to reach a high level of 50 Gm. per hour during the latter part of the month.

April showed a rising basal metabolic rate which continued into the first week of May. Accompanying this increase, the insensible perspiration remained at or near 50 Gm. per hour during the month,

only to fall during May in direct proportion to the fall in the basal metabolic rate, both, however, showing a terminal rise.

As was noted in a study of the pulse rate in this same case, the first two months of the experiment did not show a very close correlation between the basal metabolic rate and the insensible perspiration, but by the third month (February) the two curves had "settled down" and thereafter varied quite directly with one another for the remainder of the record.

The lowest sustained level of insensible perspiration was in February, during which time the lowest room temperatures were also recorded, but other than in ruling out visible perspiration, the exact significance is not at the moment apparent.

Figure 2 contains a composite graph, which shows three curves. The first curve is the basal metabolic rate as measured by the usual respiration method; the second curve is the insensible perspiration in grams per hour as measured on the day of the indicated basal metabolic rate determination, and the third curve is compiled from the statistics of Benedict and Root, indicating the calculated insensible perspiration as predicted from the basal metabolic rate. While there is no close check between individual observations, the observed insensible perspiration and the calculated insensible perspiration follow the same general trend, and both vary roughly with the basal metabolic rate.

#### SUMMARY

The body weight, taken in the evening and in the morning, has been carefully recorded over a period of one hundred and sixty-six consecutive days. From this record the total overnight and average hourly loss from the insensible perspiration have been measured. The loss by individual hours has not been recorded. It has been found that the loss over any given period of time is proportional to the size (surface area) of the person and to the basal metabolic rate. The room temperature seems to have relatively little influence. In a person weighing from 60 to 70 Kg., the loss from insensible perspiration varies from 300 to 600 Gm. overnight, or from 30 to 60 Gm. per hour, even during rest or sleep. The loss per hour varies constantly but not too definitely with the basal metabolic rate, frequent determinations of which have been made. A more extensive study of both normal subjects and persons with metabolic disorders will probably give averages from which it will be possible to estimate the basal metabolic rate accurately and easily by merely measuring the loss in weight by insensible perspiration over a short period, instead of by the present rather uncomfortable respiration method. From values obtained in this experiment and values obtained by Benedict and Root, an increase of 1 Gm. per hour

of insensible perspiration is approximately equivalent to 30 calories per twenty-four hour increase in the basal metabolic rate.

#### CONCLUSIONS

1. There is a definite loss in body weight through evaporation of water from the skin and lungs, without visible perspiration.

2. This loss in weight varies with the surface area of the subject and is also dependent on the basal metabolic rate.

3. The loss in weight may amount to 600 Gm. overnight or to as much as 60 Gm. per hour, even during sleep.

4. A loss of 1 Gm. from insensible perspiration is the approximate equivalent of 30 calories per twenty-four hours.

5. It is possible and feasible to compute the basal metabolic rate by measuring the loss in weight due to insensible perspiration.

6. The findings of Benedict and Root have been extended and verified.

# THERAPEUTIC APPLICATION OF ACIDOPHILUS MILK IN SIMPLE CONSTIPATION

A REPORT OF THIRTY-SIX CASES

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Acidophilus milk as originally devised by Rettger and Cheplin in 1922<sup>1</sup> was the culmination of a series of efforts to establish a culture medium for the growth and study of *Bacillus acidophilus* which would preserve a high degree of viability of the organism and serve to meet various experimental and practical needs. Intensive search during the past ten years by various laboratories for a substitute possessing the merits of acidophilus milk in a form that would be more readily portable and with a potency relatively permanent has not attained any degree of success, so far as we are aware.

The principle of acidophilus therapy is based on the following well known observations: 1. *B. acidophilus*, or a closely related aciduric organism, constitutes the bulk of the intestinal flora of breast-fed infants. 2. The oral administration of lactose or dextrin to man and lower animals stimulates the development of *B. acidophilus* in the intestine. 3. Appropriate cultures of *B. acidophilus* (accompanied by ample amounts of milk, lactose or dextrin), when taken by mouth, survive passage through the digestive tract; in this respect they differ most markedly from *B. bulgaricus*. 4. No evidence is at hand to show that this organism and the metabolic products formed by it in any known medium are in the least harmful to the host when taken by mouth.

In their early investigation of the therapeutic properties of acidophilus milk, Rettger and Cheplin conducted experiments on twenty ambulant patients with conditions as follows: constipation, ten (including one with enteroptosis); chronic diarrhea following an attack of bacillary dysentery, two; colitis, three; sprue, two, and eczema, three. The treatment with acidophilus milk brought at least temporary relief to a

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From the Department of Bacteriology, Yale University.

1. Rettger, L. F., and Cheplin, H. A.: *Bacillus Acidophilus* and Its Therapeutic Application, Arch. Int. Med., 29:357, 1922.

large majority of these subjects. Although the patients were sent to the laboratory by various physicians, and although considerable cooperation was received from physicians, some criticism was directed against the work because it was carried out entirely by investigators who were not members of the medical profession.

A large number of bacteriologic and clinical investigations have since been carried out by various other investigators. A fairly complete bibliography of these, with brief abstracts of the work done up to 1931, has been published by Frost and Hankinson.<sup>2</sup> A perusal of this volume shows that the clinical results reported by different authors are, on the whole, favorable to the acidophilus therapy. However, the principle has met with considerable abuse at the hands of both the producers of acidophilus products and the physicians, with the result that there has been some undermining of confidence in the principle.

The abuse originated in a large measure because of the flooding of the market with numerous so-called acidophilus products which belied the labels they carried. Few contained *B. acidophilus* or any other aciduric organism in appreciable numbers at the time of purchase; others which boasted of cultures of high viability contained, in place of the accepted intestinal aciduric type, an organism which resembled certain common oral or dental strains. Many of these products were marketed in the form of concentrates varying from pastes, powders, tablets and candies to cultures and suspensions in broth, whey and fruit juice. The concentrates, when they contained the organism indicated on the labels were, as a rule, prescribed in such small doses as to be useless for the intended purpose. These substitute products, particularly the so-called concentrates, because of the ease with which they could be prescribed and administered, found many willing advocates and buyers who demanded an article obtainable in pillboxes or medicine vials rather than one that is supplied in massive viable liquid culture.

Acidophilus treatment, to be at all effective, must involve the administration of massive doses of cultures of *B. acidophilus*. Furthermore, favorable results should be expected only when the large doses of cultures are accompanied by relatively large amounts of lactose or of milk as a lactose vehicle. Unfortunately these long-established points have been too generally overlooked or ignored.

Unfortunately also the acidophilus principle has frequently been applied in cases in which there has been failure to yield to other treatment, and attempts have been made to relieve symptoms and conditions which are not directly or even indirectly the result of intestinal derangement. In 1922 Rettger and Cheplin wrote as follows: "This (acidophilus treatment) is not a cure for all kinds of ailment, nor will all

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2. Frost, W. D., and Hankinson, H.: *Lactobacillus Acidophilus*, Milton, Wis., Davis-Greene Corporation, 1931.

cases of disturbances falling within its category necessarily respond to the acidophilus treatment. It is not an elixir in the sense that Metchnikoff's *B. bulgaricus* was for a while supposed to be. The ingestion of relatively few acidophilus bacilli will not lead to implantation and bodily improvement." Since then the same precaution against unwarranted optimism has been urged again and again by the same laboratory.

In the investigation reported here, the authors attempted to select cases of simple constipation, that is, cases which were not complicated by any other known derangement. In several instances the factor of a nervous temperament could not be eliminated, and three subjects had had an operation on the gallbladder. Attempts were also made to select patients who had apparently led a more or less normal life. The patients were all ambulant, and no restrictions as to diet were imposed.

#### MATERIAL AND METHODS

All the cases reported in this paper were supplied by Dr. Levy from his private practice, together with a record of the routine physical examination and the history of each patient. The chief symptom of the subjects was chronic constipation, with more or less of the usual syndrome, which was relieved only by the continued use of cathartics. Throughout the course of treatment with acidophilus milk the patients were examined at frequent intervals. The patients were ambulant at all times.

The only change introduced into the diet was the ingestion of 1 quart (956 cc.) of acidophilus milk daily. Occasionally this amount was reduced as a matter of expedience. The viability of the acidophilus cultures in the milk was checked at frequent intervals and was always found to be high. All the patients were requested to discontinue the use of cathartics as soon as they started the milk treatment. They were instructed, however, to resort to an enema of warm (100 to 102 F. [37.7 to 38.8]) physiologic solution of sodium chloride if and when they experienced any discomfort owing to a failure to evacuate the bowel over a period of several days. This expedient was to be followed until natural evacuations were induced through the acidophilus milk treatment.

In order to eliminate as much as possible the element of suggestion, each of the patients was made to understand at the outset that the proposed treatment was purely experimental and that not too much should be expected of it. In other words, the aim was to keep the subjects in a more or less doubting or critical attitude of mind instead of an overoptimistic one. However, the fullest cooperation was urged at all times.

Immediately preceding the first administration of the acidophilus milk, fecal specimens were subjected to the usual physical and bacteriologic examination,

which constitutes an important adjunct in experiments of this type. Similar fecal examinations were made at least once a week in the Yale laboratory of bacteriology, following the first ingestion of the milk. The laboratory procedure included the following: (1) study of the physical character of the stool, i. e., the consistency, odor, color and chemical reaction ( $p_H$ ); (2) microscopic examination of the feces for parasites, and approximate determination of the relative numbers of gram-positive rods resembling intestinal *B. acidophilus*, and (3) plating of the feces on special agar, with a standard 4 mm. loopful of definitely emulsified and diluted feces.

The plating was done on tomato-yeast-peptonized milk agar, and the plates were incubated for forty-eight hours in an atmosphere containing 5 per cent carbon dioxide. Examination of the plates consisted in counting at least 100 colonies on each plate and determining the approximate percentage of acidophilus-like colonies. The laboratory stock strain, Scavano, which was the one regularly fed to the patients, was used as a basis for comparison.

Every patient was visited at least once weekly for a study of the results of the treatment as shown both by the physical condition and by the mental attitude of the subject. At these times the fecal samples were collected for examination in the laboratory. Every patient was instructed to keep an accurate record of the bowel movements and of any changes in conditions which occurred between visits.

After the milk treatment was begun, it was continued for at least eight to ten weeks, if the results were positive. At this point, and when a daily bowel movement was established, the milk treatment was interrupted, and the number of bowel movements per week and the general condition of each patient were carefully noted during the following "rest period."

As a rule, in patients who responded favorably there was a more or less gradual return to the abnormal condition until the second or third week after the first interruption of the milk treatment. When the constipation became sufficiently aggravated to require resort to the customary cathartic, the milk treatment was resumed. It was continued for from six to eight weeks and then was again interrupted. With each completion of such a phase the favorable effects of the treatment appeared to be increasingly prolonged. This program of alternate consumption of acidophilus milk and interruption was continued until the relief remained "permanent" for at least from twelve to sixteen weeks after the last ingestion of the milk. When this stage was reached the subjects were released from the experiment, although, in some instances, more or less contact with them was maintained. The patients were continually under observation, and regular fecal examinations were made during the period in which the treatment was temporarily interrupted, as well as when it was being continued.

Patients who did not react favorably to the treatment within from four to six weeks after the beginning were regarded as showing negative results, and the treatment was discontinued.



Throughout the investigation evidence of a relatively permanent implantation of *B. acidophilus* was sought. To this end the feces of persons who responded favorably to the regimen and who seemed to have acquired prolonged or permanent relief (lasting at least sixteen weeks after the last acidophilus milk feeding) were repeatedly examined, and attempts were made to isolate *B. acidophilus*. Persons from whom isolations were obtained which were of the X colony type and which resembled the Scavano (ingested) type are referred to temporarily as "implanters." Considerable additional study of the aciduric organisms isolated from these subjects will be necessary, of course, to show definitely that the organisms isolated are identical with or resemble the organism administered in the acidophilus milk.

The total number of persons treatment of whom was attempted in this investigation was fifty-four. Eighteen of these were dismissed before the end of the first four weeks for various reasons, such as their dislike of the milk, their failure to follow instructions and to enter into full cooperation and their habits of living. Some of these promised clearly negative results; others, and perhaps a large majority, gave slight indications of responding favorably at the time the treatment was discontinued. None of the eighteen subjects who were dismissed is included in this report.

#### POSITIVE RESULTS

Twenty-seven of the thirty-six patients, or 75 per cent, responded positively to the treatment. These patients had a history of simple constipation. However, three of them had had an operation on the gall-bladder, as a result of which they experienced more or less discomfort when they were constipated. All were without definite nervous symptoms. None of this group of twenty-seven patients was undergoing medication when first seen, except for the relief of constipation. Medication, aside from the use of acidophilus milk, was discontinued immediately after the beginning of the experiment. Examination of the feces by the direct plating method before the first milk feeding failed to demonstrate the presence of *B. acidophilus* in the stools of twenty-four of the subjects. Three were found to harbor an acidophilus-like organism in the intestine in numbers ranging from 15 to 45 per cent of the total cultivable flora, as revealed on the agar plates. Strange to say, the acidophilus count for each of these three subjects dropped to zero during the first two weeks of acidophilus milk treatment, after which it started to rise.

Some abdominal distention and discomfort were experienced by the subjects during the first two weeks of the milk treatment. Alleviation of the constipation usually occurred as soon as the distention disappeared. The relief was not immediate. The bowel movements gradually became more frequent, the feces acquiring a softer texture or con-

sistency and a lighter color. A normal daily bowel rhythm was established within from two to four weeks after the beginning of the treatment. The favorable change was correlated in general with an increase in the *B. acidophilus* content of the intestine, the counts on the plates, after the earlier rises, varying between 60 and 90 per cent.

The milk treatment was discontinued in all the patients within from eight to twelve weeks following the first feeding. Within a period of four weeks all but five patients had apparently lost the benefit of the treatment and were obliged again to resort to cathartics. The milk treatment was resumed. It was continued for from six to eight weeks and then was again discontinued. In the cases in which beneficial results were maintained for from twelve to sixteen weeks following the second *acidophilus* milk feeding, as revealed by the bowel movements, the general condition of the subjects and the occurrence of appreciable numbers of *B. acidophilus* in the feces, attempts were made to isolate *B. acidophilus* from the stools, with the hope of demonstrating so-called permanent implantation of the administered strain in the intestine.

In a few instances a third course of *acidophilus* milk treatment was necessary before protracted relief was established following discontinuance of the milk; and in one case, which was of particular interest, four such courses were found necessary to prevent the recurrence of constipation within sixteen weeks after the last administration of the milk.

It was observed invariably that, on a return of the subjects to an abnormal condition of the bowels during the rest periods, the *acidophilus* counts for the feces underwent marked decreases. After resumption of the milk feeding the constipation was relieved within a week, and the *acidophilus* count rose rapidly. In patients who were apparently "permanently" relieved there was always a relatively high percentage of *B. acidophilus* in the feces, the mean average for the group ranging between 50 and 60 per cent.

Fourteen of the twenty-six patients who responded positively, or 38.9 per cent of the entire group, were found, after two or more milk feedings and subsequent rest periods, to be so-called implanters; that is, they carried *B. acidophilus* in appreciable numbers in the intestine for at least from twelve to sixteen weeks after the last treatment. Isolations were made of the aciduric<sup>3</sup> organism carried by them. A study for the purpose of identifying these strains and of discovering their exact relation to the fed aciduric type or strain is now under way. Morphologically and in certain cultural reactions the isolated organisms resemble the Scavano strain which was used in the preparation of the administered *acidophilus* milk. Some time will be required before a final conclusion as to their identity can be drawn.

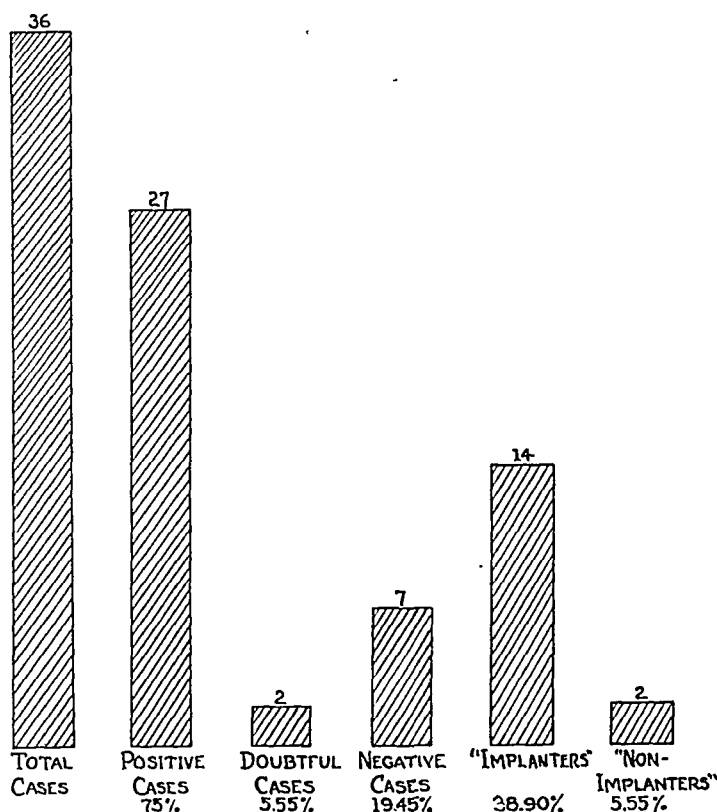
Two of the subjects in the group of twenty-seven who responded positively, or 5.55 per cent, were still free from constipation sixteen

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3. In this paper the term aciduric refers to aciduric bacillary forms only.

weeks after the end of the last period of treatment, but it was impossible to isolate an aciduric organism from their stools owing to the relatively small number present. One of these patients suffered several months later from a return of the constipation. Subsequent treatment again elicited a favorable reaction.

Eleven of the subjects who responded positively are still undergoing treatment. Some are in their second course of alternate treatment and rest. Further study of these, it is anticipated, may reveal their falling sooner or later into the group of persons who are referred to in this paper, for convenience, as implanters.



Graph showing results of feeding acidophilus milk in thirty-six cases of simple constipation.

#### HISTORY OF SIX REPRESENTATIVE CASES IN WHICH POSITIVE RESULTS WERE OBTAINED

Space does not permit a detailed account of each of the twenty-seven cases which gave positive results. The following selected histories are presented as fairly representative. In all these, the medical history, both past and present, was essentially without significance.

CASE 1.—A white woman, 25 years of age, had a definite history of simple constipation extending over a period of ten years. Preliminary examination of the feces revealed no acidophilus-like organism. The stools were dark, firm, foul-smelling and alkaline. Within the first two weeks of consumption of acidophilus

milk (1 quart daily) the aciduric flora of the feces attained a proportion of 70 per cent of the total viable flora. This was accompanied by marked relief from constipation, the subject having at least one free movement of the bowels a day without the use of the customary or of any other cathartic. The daily amount of acidophilus milk was reduced, at the patient's request, to 1 pint (473 cc.). The milk feeding was continued for nine weeks, during which time the acidophilus count ranged between 60 and 90 per cent of the total viable intestinal flora and the patient continued to have at least one movement of the bowels a day.

At the end of the ninth week the milk treatment was interrupted for six weeks. There was a gradual return to the constipated condition; the movements of the bowels were reduced to about three per week, and the acidophilus count for the stool fell to between 15 and 40 per cent. The milk treatment was resumed and was continued for eight weeks. During this period the constipation was again completely relieved and the intestinal aciduric flora predominated to the extent of 65 to 90 per cent of the total viable flora. At the end of the eighth week the milk treatment was again discontinued. The patient was seen twice weekly, and two fecal examinations were made each week for sixteen weeks. Throughout this period the subject remained entirely free from constipation, and a high count of the acidophilus flora was maintained. An acidophilus-like organism was isolated from the stool of this patient late in the second period of nonfeeding.

CASE 2.—A white man, 28 years old, had had constipation for about six years. Preliminary fecal examination failed to reveal *B. acidophilus*. The patient took a quart of acidophilus milk daily for eight weeks. During the first two weeks he complained of marked abdominal distention and discomfort; there was no relief from the constipation except by enemas. The acidophilus count was low (from 15 to 40 per cent). Immediately following these two weeks the constipation was relieved and the acidophilus count for the stool rose and remained between 75 and 90 per cent as long as the milk feeding was continued.

At the end of the twelfth week the milk treatment was discontinued for twelve weeks, during which time the patient was visited twice a week. A medical examination was given once a month, and two fecal examinations were made weekly. During this rest period there was no return of the constipation and the acidophilus count for the feces did not fall below 70 per cent of the total viable flora. At the end of this period *B. acidophilus* was isolated from the stool and the subject was not kept under further observation.

CASE 3.—A white man, 32 years old, had had constipation for about seventeen years. Examination of the stool before treatment revealed no acidophilus-like organisms. During the first three weeks of acidophilus milk treatment the subject complained of moderate abdominal distention and discomfort; the constipation was marked, and the acidophilus counts for the stool remained very low. Immediately following this period the constipation was relieved rapidly and the aciduric count increased. The ingestion of the milk continued for six more weeks, during which time the patient had at least one free bowel movement per day and the acidophilus flora ranged from 65 to 85 per cent. After nine weeks the milk treatment was discontinued. The relief from constipation persisted for sixteen weeks, and the aciduric flora maintained a level of from 25 to 90 per cent of the total cultivable flora. An acidophilus-like organism was isolated from the feces, and the patient was released from further observation.

CASE 4.—A white woman, aged 60, had been subject for about two years to constipation uncomplicated by any other known physical ailment. The patient possessed a nervous temperament. Preliminary examination of the feces revealed the presence of acidophilus-like organisms which formed 60 per cent of the viable

flora. During the first two weeks of consumption of acidophilus milk the constipation was only slightly relieved and the number of aciduric bacilli in the stool fell to 25 per cent. Definite relief occurred early in the third week, when the acidophilus count rose to from 75 to 95 per cent. The milk treatment was discontinued at the end of the eighth week. Within two weeks the constipation asserted itself again. This was paralleled by a drop in the fecal acidophilus count to a low level. The rest period covered six weeks, at the end of which acidophilus milk was again given. Rapid relief followed the resumption of the treatment, accompanied by a correspondingly rapid rise in the acidophilus content of the stool. The second course of treatment was continued for eight weeks. Following its final interruption, the subject was held under observation for fourteen weeks, during which time there was no return of the former condition. A relatively high acidophilus count was maintained during this entire period. An acidophilus-like organism was isolated from the stool near the termination of the final period of observation.

CASE 5.—A white woman, aged 40, had had apparently simple but obstinate constipation for ten years. She was relieved only by large doses of strong cathartics. No acidophilus-like organisms were demonstrable in the feces before the beginning of the acidophilus milk treatment. The patient received 1 quart of the milk daily. Relief was slow, requiring almost four weeks of treatment; the acidophilus counts were increased from 25 per cent at the end of the first week to 90 per cent at the end of the fourth week. The first course of treatment continued for fourteen weeks, during the last eight of which the subject had at least one bowel movement a day and the aciduric flora continued to show a high count.

At the end of the fourteenth week the milk treatment was discontinued for four weeks. During this rest interval the acidophilus count dropped to zero and the constipation returned. Use of the milk was resumed and was continued for eight weeks. Complete relief from the constipation again followed, with a high percentage of acidophilus flora. A second rest period followed. Within two weeks the constipated condition again returned and the percentage of aciduric flora dropped to zero. The milk treatment was discontinued for four weeks until the constipation had become marked. At the end of the four weeks' rest, the milk treatment was resumed and was continued for eight weeks. The symptoms again disappeared, accompanied by a high percentage of aciduric flora. The milk was discontinued, and again the acidophilus count fell to zero, this time within three weeks. The count remained at zero during the entire subsequent period of observation. However, the relief from constipation persisted, the patient reporting at least one free bowel movement per day. This condition continued to the end of the fourteenth week following the last milk feeding, when the subject was dismissed as relieved.

CASE 6.—A white youth, aged 16, had suffered from constipation for two years. Examination of the stool before the beginning of the treatment revealed an acidophilus-like organism constituting about 45 per cent of the total cultivable intestinal flora. The subject received 1 quart of acidophilus milk daily for ten weeks. During the first week the content of acidophilus-like flora fell to zero and there was no relief from the constipation. During the second week the count rose to 70 per cent, accompanying a marked improvement in the subject's condition, and relief from the constipation was complete.

The milk treatment was discontinued at the end of the tenth week and was not again resumed. The patient was kept under observation for sixteen weeks following the last ingestion of acidophilus milk. During this entire period there was no return of the constipation, and the acidophilus count for the feces varied from 25 to 90 per cent.

## NEGATIVE RESULTS

Seven of the twenty-six persons under observation, or 19.45 per cent, failed to respond to the milk treatment. Even after they had taken the milk for from four to twelve weeks, no relief from constipation could be observed.

Two of these seven subjects were on the acidophilus milk regimen for eight weeks. In one there was an acidophilus-like intestinal flora of 95 per cent before the first ingestion of the milk. This was quickly reduced to zero after the beginning of the treatment and remained at a low level throughout the course. At no time during the treatment did the acidophilus count for the stool rise above 20 per cent. The other subject obtained but slight relief even when the acidophilus count rose as high as 85 per cent during an eight weeks' course of feeding. The character of the stools of both these subjects remained unaltered, being at all times firm, dark, foul-smelling and alkaline in reaction, except when the patient was temporarily relieved by the customary cathartic.

Three others failed to respond clinically and to acquire an acidophilus flora in the intestine, even after from four to six weeks of milk ingestion. In two of these subjects the treatment was discontinued after four weeks; in the third subject it was discontinued after six weeks.

One patient, an ex-service man, whose condition had been diagnosed at several veterans' hospitals as markedly neurotic, was admitted to the investigation at the request of the Red Cross. Physical examination revealed a sacro-iliac strain, an old appendectomy scar and scars from hemorrhoidectomy and repairs of a rectal fistula. The patient complained of various aches and pains in the abdomen, chest and back, and of chronic constipation from which relief could not be obtained even by the use of strong cathartics. Soapy water enemas appeared to be the only means of obtaining relief.

This patient received acidophilus milk for sixteen weeks, during which time he reported no improvement in the constipation. From the second to the last week the acidophilus counts for the stools remained high, being 70 to 95 per cent. During the entire period the subject reported that he had to resort to strong cathartics and soapy water enemas to effect elimination. There is, however, a reasonable measure of doubt as to whether he was truthful in reporting the bowel movements and his general condition. The case was regarded as unsatisfactory from all angles.

The last of the seven patients in whom the milk treatment gave negative results responded positively to the treatment during the first two weeks. The stools became soft, light in color and inoffensive in odor, and the acidophilus count rose as high as 90 per cent. At the outset no acidophilus-like organisms could be demonstrated. After the

first two weeks the patient again became very constipated, and the acidophilus count dropped to zero. After six weeks of unsuccessful treatment the patient was dismissed.

#### DOUBTFUL RESULTS

Two of the thirty-six patients, or 5.55 per cent, reacted in such a manner as to leave the results doubtful. They were for a time relieved and then suddenly experienced a return of the constipation. After the constipation had continued for from one to three weeks, normal daily bowel rhythm was restored more or less suddenly.

A possible explanation for the doubtful or variable response in one of these two patients may be found in his alcoholic tendencies. He admitted the use of 1 quart of raw whisky on some days. These spasmodic bouts of intemperance were correlated closely with the periods of extreme constipation. So long as the patient abstained from alcohol and drank the acidophilus milk he had at least one daily bowel movement of a more or less normal character and the acidophilus count was high. Indulgence in alcoholic drinks resulted again in the old type of constipation and in a low acidophilus content in the feces. The drinking episodes were associated with a complete loss of appetite. All attempts to induce the patient to avoid them failed, and he was dropped from the investigation.

In the other doubtful case no explanation could be found for the sudden reversions to constipation. The patient apparently led a normal, well ordered life and was addicted to no bad habits. While the acidophilus milk caused relief for periods ranging from six to eight weeks, during which the stools were normal and the acidophilus count was high, the old symptoms recurred suddenly, accompanied by a corresponding change in the character of the feces and a marked reduction in the acidophilus count. The relapses continued for periods of from two to four weeks during continued acidophilus treatment. The constipation then vanished with the same degree of suddenness with which it had recurred. After four periods of relapse, the patient was dismissed.

#### COMMENT

The present clinical and bacteriologic investigation has been in progress about fifteen months. Additional data will be incorporated in a future publication which, it is hoped, will cover various phases of the study of lactobacilli.

The investigation has served to show thus far that simple, uncomplicated constipation should be readily amenable to treatment with acidophilus milk in at least 75 per cent of the patients subjected to the regimen, provided a so-called standard viable culture milk is employed and provided the amounts administered daily are appreciable (from a pint to a

quart, depending on the tolerance and idiosyncrasy of the patient). It is desirable, also, that the milk be taken in three or four portions daily, preferably between meals. In some instances, from 1 to 3 ounces (31.1 to 93.3 Gm.) of lactose added to the daily milk feedings is a material aid in enhancing the results.

The present study has shown not only the importance of long continued administration of the acidophilus milk, but also that of periodic interruption for several weeks, followed by resumption of the treatment for relatively long periods. By this system of alternate feeding and rest it was possible to bring about favorable clinical results and apparent implantation, which persisted in a large percentage of the cases over relatively long periods of time. A general inquiry into the diet of the patients elicited the information that the "implanters" included in their daily regimen at least moderate amounts of ordinary milk, or breadstuffs and potato, or all three of these articles of diet. This phase of the problem is receiving further study.

Rettger and Cheplin concluded, on the strength of their observations, that a favorable clinical response and implantation of the aciduric organism by acidophilus milk treatment, when they occur, are caused by the acidophilus bacillus itself rather than by the acid present in the milk or by the milk alone. Cannon,<sup>4</sup> in 1923, held to the view that the increase in acidophilus flora caused by feeding lactose in large amounts is the result of the acidity produced in the intestine rather than of the direct influence of the lactose on the aciduric organisms.

The ingestion of lactose in sufficient amounts to cause a pronounced acidic condition (lowered  $p_H$ ) in the intestine undoubtedly has a stimulating effect on the aciduric flora of the intestine. However, such an explanation is far from complete and could not account for the so-called permanent implantation in the cases reported in this paper. Kopeloff,<sup>5</sup> in 1924, showed that sterile milk or acidophilus milk freed from the bacilli does not bring about the same reaction in the intestine as does acidophilus milk. In our own work the need of large numbers of viable *B. acidophilus* has again and again impressed itself on us, particularly in the more recent investigations.

It must be recognized that some subjects do not respond to acidophilus milk treatment, even when unduly large amounts are taken daily. The same observations have been made again and again in regard to lactose, in attempts to change the intestinal flora. No explanations for these idiosyncrasies are attempted here.

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4. Cannon, P. R., and McNease, B. W.: Factors Controlling Intestinal Bacteria. Influence of Hydrogen-Ion Concentration on Bacterial Groups, *J. Infect. Dis.* **32**:175, 1923.

5. Kopeloff, N., and Beerman, P.: Nature of *Bacillus Acidophilus* Therapy, *Arch. Int. Med.* **33**:55, 1924.



The present investigation offered unusually favorable conditions for scientific and clinical study. In the first place, the subjects were all patients of a private medical practice, whose clinical records were available, and who, after the experiments began, were not undergoing any other treatment or medication and were entirely under our supervision and control. Furthermore, the work was broadly cooperative and was participated in by a physician, on the one hand, and by nonmedical scientific investigators, on the other. Finally, the subjects were all ambulant. They were visited regularly in their homes, and the acidophilus treatment was such as could be carried out in any private home.

We are fully appreciative of the difficulty involved in attempting to offer an intelligent explanation of the condition commonly termed constipation. Many objections have been offered, perhaps justly, to the expressions "autointoxication" and "intestinal putrefaction," and until more scientific evidence has accumulated to show that such processes take place in the intestine to any appreciable extent, these terms should be used with the greatest reservation or, indeed, not at all. However, that certain organisms which are present in the intestine may, under certain environmental conditions, alter the nervous and muscular mechanisms in such a way as to slow up peristalsis and, perhaps, the glandular functions, is a theory which cannot be dismissed lightly.

Acidophilus milk therapy has certain disadvantages. There are persons who have a natural dislike for sour milks. However, many of them with more or less effort have overcome this dislike. Administration in large quantities is necessary to obtain results; but when one considers that acidophilus milk is a food, possessing important properties, and that it is not in the usual sense a drug, this objection should not have much weight. Some opposition to the milk treatment is aimed at the cost. It should be stated here, as a rejoinder, that, with few exceptions, the cost does not exceed that of the high grades of certified milk.

No one can appreciate more than we the desirability of an acidophilus product combining all the important features of acidophilus milk, which could be supplied in small bulk, in which the organism would remain viable over a reasonable period of time and which would be relatively low-priced. However, owing largely to the nature of intestinal *B. acidophilus*, no such product has, to our knowledge, been forthcoming. So-called substitutes have flooded the market and have done serious harm because they have, with rare exceptions, violated the principle underlying acidophilus therapy.

#### SUMMARY

Thirty-six patients suffering from simple chronic constipation were treated with acidophilus milk the cultures of which were known to be

of high viability. All were ambulant and had been under the medical care of one of us (Dr. Levy). Of the thirty-six patients who underwent the treatment, twenty-seven, or 75 per cent, reacted favorably; seven, or 19.5 per cent, responded negatively, and in their cases the treatment was regarded as having failed. Two, or 5.5 per cent, gave results that were neither positive nor negative.

Of the patients who responded positively, fourteen, or 38.9 per cent, were so-called "implanters," that is, they maintained a high acidophilus content in the intestine for from twelve to sixteen weeks after the discontinuance of the last course of milk treatment. During this rather protracted period of high percentage of acidophilus flora no return to the former condition of constipation was noted. Two other patients, or 5.5 per cent of the entire group, showed distinct improvement sixteen weeks after the cessation of the treatment, but *B. acidophilus* was not demonstrable in their feces.

The results indicate that the most favorable, i. e., the most protracted, response will be obtained by the continued use of the milk over reasonably long periods, with interruptions (so-called rest periods) of from four to twelve weeks or even longer. Whether the administered aciduric organism actually becomes implanted in the bowel of the patient who responds positively after many weeks of feeding and intermission, or whether the constant application of the acidophilus milk under favorable conditions of diet (with milk, lactose or dextrin) stimulates to activity similar or closely related strains native in the intestine must be left an open question. Either of these two eventualities should lend strong support to the acidophilus principle.

In conclusion, we wish to state again that the words "implantation" and "implanters" are used relatively only and that no claim is made of absolutely permanent implantation of *B. acidophilus* and ensuing freedom from the recurrence of constipation. The terms are applied to certain successfully treated conditions to indicate that during and at the end of the final period of observation of from twelve to sixteen weeks following the last ingestion of acidophilus milk the plate counts for acidophilus bacilli were still relatively high and the former abnormal intestinal condition had not recurred.

# CINCHOPHEN POISONING

## REPORT OF TWO CASES WITH HISTOLOGIC OBSERVATIONS

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Cinchophen, or atophan as it was originally named, was first introduced as a drug in 1908 by Nicolaier and Dorhn,<sup>1</sup> who were able, by its use experimentally in animals and in man, to increase definitely the endogenous formation and excretion of uric acid. Owing to its spectacular ability to relieve pain in certain arthritic conditions, it was soon widely used in all types of neuritic and arthritic distress. So universal has its use become that, at present, it is being employed freely by the laity without any medical supervision.

Chemically, cinchophen is 2-phenylquinoline-4-carboxylic acid. Although it is known to have a cholagogic effect in dogs, its mode of action has not yet been definitely determined. Brugsch and Horsters<sup>2</sup> expressed the belief that cinchophen owes its cholagogic effect to direct stimulation of the hepatic cells, and they were able experimentally to show an increase in the twenty-four hour total excretion of bile and bile pigments. This action has been utilized in the intravenous administration of di-iodo-atophan for visualization of the gallbladder in diagnostic cholecystography.

Phenylcinchoninic acid under the names of cinchophen, atophan and quinophan have been most frequently reported as the cause of toxic symptoms. Other closely allied preparations that have been similarly reported on are atophanyl, biloptin (di-iodo-atophan), oxyliodide, neo-cinchophen, tolysin (a proprietary brand of neocinchophen), farastan, atoquinol and weldona tablets.

The toxic symptoms have been classified into four groups: (1) skin manifestations (rashes, pruritus and urticaria), (2) anaphylactoid reactions (shock states), (3) gastro-intestinal disturbances (nausea, vomiting and diarrhea) and (4) involvement of the liver, as evidenced by jaundice.

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From the Department of Pathology, School of Medicine, University of Pittsburgh and the Pathological Laboratories, Mercy Hospital.

1. Nicolaier, A., and Dorhn, M.: Ueber die Wirkung von Chinolincarbon-säuren und ihrer Derivate auf die Ausscheidung der Harnsäure, *Deutsches Arch. f. klin. Med.* **93**:331, 1908.

2. Brugsch, T., and Horsters, H.: Cholereise und Choleretica, ein Beitrag zur Physiologie der Galle, *Ztschr. f. d. ges. exper. Med.* **43**:714, 1924.

That cinchophen is definitely toxic to liver cells is well known now, but its toxic principle has not as yet been clearly defined. There are both a benzene ring and a pyridine ring present in the quinoline nucleus, with phenol present in combination. Sutton<sup>3</sup> expressed the belief that the toxic action is due to the formation in the body of nitrobenzenes or nitrophenols, since the higher nitrocompounds are very toxic and produce jaundice. Willcox<sup>4</sup> is of the opinion that free benzene is the toxic principle. The lesion in the liver in cases of cinchophen poisoning is similar to that due to trinitrotoluene as described by Haythorn<sup>5</sup> in 1918.

It is in the cases which involve the liver that serious and even fatal poisoning occurs. Clinically, the course is one of a progressive, although it may be intermittent, painless jaundice. Indigestion frequently precedes the jaundice, and vomiting may also occur. The liver is found enlarged at the onset, but soon decreases in size. All the secretions of the body are bile-stained, though the feces may at times contain bile. An increased amount of serum bilirubin is always present. Toxemia is progressive, and generalized edema appears before death.

The dose of cinchophen necessary to cause death is exceedingly variable. Evans'<sup>6</sup> patient had taken only 15 grains (0.97 Gm.) when signs of toxicity appeared, while Hench and Rountree<sup>7</sup> observed a man who took over 7,800 grains (507 Gm.) of cinchophen over a period of eighteen years without any discomfort or disability. The contrast in tolerance of the drug in these two cases suggests that idiosyncrasy may play some part in cinchophen poisoning. Such factors as an antecedent history of disease of the gallbladder, cirrhosis of the liver, pregnancy or conditions favoring decreased glycogen content of the liver, such as starvation, malnutrition, chronic infection or fever, are thought by many to predispose to an intolerance to the drug.

Because the drug is known to be toxic, many modes of administration have been employed, but none has been found that make the use of the drug entirely safe. Thus, toxic symptoms have appeared though much water was taken with the drug or though it was given with equal or larger doses of sodium bicarbonate. The giving of the drug in inter-

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3. Sutton, D. C.: Acute Yellow Atrophy of the Liver Following the Taking of Cinchophen, *J. A. M. A.* **91**:310 (Aug. 4) 1928.

4. Willcox, W. H.: Atophan Derivatives in Rheumatism, *Brit. M. J.* **2**:273 (Aug. 7) 1926.

5. Haythorn, S. R.: The Pathology of Trinitrotoluene Poisoning, *Internat. A. M. Museums Bull.* **7**:1 (May) 1918.

6. Evans, G.: Atophan Derivatives in Rheumatism, *Brit. M. J.* **2**:93 (July 10) 1926.

7. Hench, P. S., and Rountree, L. G.: In discussion on Rabinowitz, M. A.: Atrophy of the Liver Due to Cinchophen Preparations, *J. A. M. A.* **95**:1232 (Oct. 25) 1930.

mittent courses has also caused fatal reactions. The intravenous use of di-iodo-atophan in minimal amounts in roentgenography has had a toxic effect almost immediately. Withdrawal of the drug at or before the first sign of toxic symptoms does not always prevent a fatal result. In the case reported by Cabot,<sup>8</sup> toxic symptoms appeared two months after cessation of administration of the drug.

In 1913, the first cases of cinchophen poisoning, twelve in number, were reported by von Müller,<sup>9</sup> Phillips<sup>10</sup> and Herrick,<sup>11</sup> and skin manifestations were seen in all with no fatalities. The first case in which jaundice was noted was reported by Schroeder<sup>12</sup> in 1922 and was cited by Worster-Drought<sup>13</sup> in 1923. Since that time, there have appeared every year, in the literature, numerous cases of hepatic damage in which there was a history of the taking of cinchophen. Klinkert<sup>14</sup> and Kingreen<sup>15</sup> in Germany, Rake,<sup>16</sup> Loewenthal, Mackay and Lowe<sup>17</sup> in England and Cabot,<sup>8</sup> Sutton,<sup>3</sup> Rabinowitz<sup>18</sup> and Reichle<sup>19</sup> in this country have reported fatal cases with observations at autopsy. In these cases the fatal doses ranged from 37½ to 2,700 grains (1.97 to 175.5 Gm.) with intervals of from one to sixty days between the time the drug was discontinued and the time at which toxic symptoms appeared.

Autopsies of these patients showed a striking constancy and similarity of the hepatic lesions. In the majority of cases, the liver was found to be small, shrunken and finely nodular, the cut surface present-

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8. Cabot, R. C., and Cabot, H.: Case Records of the Massachusetts General Hospital, Boston M. & S. J. **192**:1122 (June 4) 1925.

9. von Müller: Nebenwirkung des Atophans, Verhandl. d. Gesellsch. f. inn. Med. u. Kinderh., February 13, 1913; abstr., Therap. Monatsch. **27**:468 (June) 1913.

10. Phillips, J.: Skin Rashes following the Administration of Atophan, J. A. M. A. **61**:1040 (Sept. 27) 1913.

11. Herrick, W. W.: A Scarlatiniform Rash from Atophan, J. A. M. A. **61**:1376 (Oct. 11) 1913.

12. Schroeder, K.: Cases of Atophan Poisoning, Ugesk. f. læger **84**:1141, 1922.

13. Worster-Drought, C.: Atophan Poisoning, Brit. M. J. **1**:148, 1923.

14. Klinkert, D.: Geelzucht als gevolg van langdurig atopaangebruik, Klin. Wchnschr. **6**:24 (Jan. 1) 1927.

15. Kingreen, O.: Vorsicht bei der Verabreichung von Dijodatophan (Biloptin), Deutsche med. Wchnschr. **53**:971, 1927.

16. Rake, G. W.: A Case of Subacute Yellow Atrophy Following the Taking of Atophan, Guy's Hosp. Rep. **77**:229 (April) 1927.

17. Loewenthal, L. J. A.; Mackay, W. A., and Lowe, E. C.: Acute Yellow Atrophy of Liver Following Administration of Atophan, Brit. M. J. **1**:592, 1928.

18. Rabinowitz, M. A.: Atrophy of the Liver Due to Cinchophen Preparations, J. A. M. A. **95**:1228 (Oct. 25) 1930; Chronic Hepatitis and Hepatolysis Following the Use of Atophan, M. Clin. North America **11**:1025 (Jan.) 1928.

19. Reichle, H. S.: Toxic Cirrhosis of the Liver Due to Cinchophen, Arch. Int. Med. **44**:281 (Aug.) 1929.

ing a stippled pattern of alternate small areas of red and yellow. The pathologic changes were most uniform, in that acute or subacute yellow atrophy was nearly always diagnosed. Reichle<sup>19</sup> called the condition in his two cases toxic cirrhosis of the liver, based on the finding of much fibrous tissue and many newly formed bile ducts. Extensive destruction of hepatic tissue was the chief histologic change in all cases.

Parsons and Harding,<sup>20</sup> early in 1931, reported four cases of death due to cinchophen, with complete observations at autopsy. In all of the cases the liver was found to be nodular, decreased in size and covered on the cut surface by raised, yellowish, soft nodules, separated by red or reddish-brown, firmer tissue. Microscopically, these livers showed necrosis of the hepatic parenchyma, fatty degeneration of the persisting hepatic cells and, along with this, changes interpreted as young fibroblastic tissue and regenerating bile ducts; hemorrhage and round cell infiltration were present. The authors designated these changes as acute yellow atrophy; but in one case in which the poisoning was of longer duration, and in which they believed that considerable fibroblastic response was shown, they called the condition toxic cirrhosis.

In May, 1931, Beaver and Robertson<sup>21</sup> of the Mayo Clinic published a review of five fatal cases in which death was due to cinchophen or one of its derivatives. At autopsy, the livers were reduced in size, but were not distorted. They were mahogany red with innumerable small yellow nodules projecting above the level of the cut surface. Histologically, in all of the five cases the liver presented the same general appearance. There was widespread necrosis of the hepatic parenchyma without involvement of the reticulum, vascular apparatus or bile ducts. The skeletons of the lobules were identified by the intact interlobular zones, sinusoids and central veins. In some lobules no hepatic cells were present, and the lobule consisted of a collapsed mass of reticulum and sinusoids with little exudative reaction. The persisting hepatic cells were arranged in irregular cords or isolated islands surrounded by collapsed sinusoids and their supporting reticulum. The cells showed granular degeneration of the cytoplasm, with vesicular and pyknotic nuclei. Many ductlike cellular structures were seen, which were composed of atrophic but surviving hepatic parenchyma and which resembled biliary ducts. These accidentally remaining columns of hepatic cells, isolated in the extensive degeneration of the parenchyma, were termed by Beaver and Robertson<sup>21</sup> "pseudotubuli." No regeneration of bile ducts or of hepatic cells was seen except in one

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20. Parsons, L., and Harding, W. G.: Cinchophen (Atophan) Poisoning: Report of Four Cases, *Am. J. M. Sc.* **181**:115, 1931.

21. Beaver, D. C., and Robertson, H. E.: The Specific Character of Toxic Cirrhosis Observed in Cinchophen Poisoning: A Review of Five Fatal Cases, *Am. J. Path.* **7**:237, 1931.

case in which death occurred five months after cessation of the use of the drug. No newly formed connective tissue was observed; the apparent fibrosis was relative, being due to the preponderance of stroma where the parenchyma had disappeared.

This report offered a new point of view in regard to the histopathology of the hepatic lesion due to cinchophen, which will be discussed later. In general, however, it is evident from the unusual uniformity of the clinical and pathologic observations that the changes induced by cinchophen intoxication are chiefly in the liver. Other lesions, such as fatty changes in the heart and kidneys, and mucosal and serosal hemorrhages, are comparatively insignificant and are probably secondary to those of the liver. Gastro-intestinal lesions have been reported in only a few instances. There is, however, some recent evidence to indicate that the gastro-intestinal changes may be second in importance only to those in the liver in this condition. This will be discussed later.

Two cases of fatal cinchophen poisoning with outstanding lesions in the liver have recently come to our notice; they form the basis for the present contribution.

#### REPORT OF CASES

CASE 1 (Courtesy of Dr. Vincent P. Hart, Waynesburg, Pa.).—Mrs. K. B., aged 42, white, married, a housewife, was seen on Jan. 7, 1932, when she complained of a progressively increasing jaundice. The illness had begun on January 1, with nausea and vomiting. Jaundice appeared two days later. The gastric symptoms abated somewhat, but the icterus increased in intensity. Catarrhal jaundice was the provisional diagnosis at this time. The patient continued to be ill, and the jaundice deepened. About January 21, the gastric symptoms reappeared and were soon so severe that hypodermoclysis and rectal feedings were necessary.

A further query revealed that about six weeks prior to her acute illness, the patient complained of myalgic pains in her arms and, on the advice of a physician in another city, procured "farastan" tablets and took seventy-five (or  $562\frac{1}{2}$  grains [36.56 Gm.] of mono-iodocinchophen), stopping only when her acute illness began. These facts established the diagnosis of cinchophen poisoning.

The accepted measures were ineffective in this case. Hemorrhages developed from venipuncture wounds, and it became impossible to maintain the patient's nutrition. After a period of delirium, the patient died on February 2, thirty-three days after the onset of acute symptoms and a little over ten weeks after the first use of the drug.

The results of laboratory tests made two days before the patient's death included an icterus index of 200, a nonprotein nitrogen of 89 and a serum calcium of 5. The urine at this time showed a cloud of albumin, numerous granular casts and pus cells, and much bile and blood.

A limited autopsy was permitted. This was done twenty-six hours after death and after the body was embalmed. It was merely an examination of the surface of the liver with removal of a small portion for section. The liver itself was believed to be somewhat reduced in size; its surface was smooth and brownish yellow. Nothing further is available concerning the gross findings.

Histologically, the liver showed chiefly a diffuse, extreme cloudy swelling and granular degeneration of the hepatic cells with disruption of the columns of hepatic cells. The usual degenerative nuclear changes were noted. The degenerative process was more marked in the centers of the lobules, where many of the cells had completely disintegrated. Those that remained contained bile pigment, evident as a fine brownish stippling. Small plugs of inspissated bile were seen occasionally in the canaliculi near the portal triads, as well as in some of the terminal bile ducts. The sinusoids did not appear engorged, though the fixation of the tissue (formaldehyde after embalming) had preserved the erythrocytes poorly. The stroma was not increased. The portal sheaths contained a scattered infiltration of polymorphonuclear leukocytes, along with a few small collections of

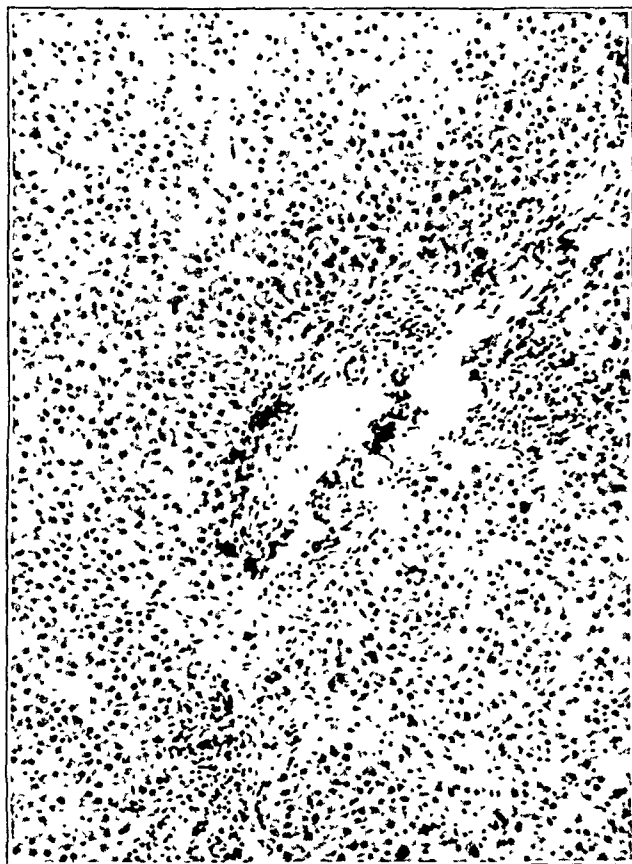


Fig. 1 (case 1).—Diffuse swelling of hepatic cells and a mild cellular infiltration. The liver showed less necrosis than in any case reported up to this time.

lymphocytes. Occasional polymorphonuclear leukocytes were present in the sinusoids.

CASE 2.—Mr. C. M., aged 60, white, a bricklayer, was admitted to Mercy Hospital on Aug. 18, 1931, with the symptoms of jaundice, nausea and heaviness in the epigastrium after meals. The past history brought out that five years previously he had an attack of nausea, anorexia, weakness and chill, with boring pain in the right upper quadrant which required morphine. Following this, he was well until June, 1931, when he sought medical attention for relief of arthritis in both knees and the right ankle. Cinchophen was prescribed in the dose of 15 grains (0.97 Gm.) three times a day, and this he took regularly for two months. It was estimated that he took in all about 2,500 grains (162.5 Gm.) of



the drug. On August 8, he was nauseated. On August 16, he noticed that his entire skin was yellow. The jaundice steadily increased, but there was no pain or vomiting. He had not taken any of the drug for two weeks before admission.

Physical examination showed a well nourished man of 165 pounds (74.8 Kg) with marked generalized jaundice but no other outstanding symptoms or signs. The only physical findings were in the abdomen, where the firm, tender edge of the liver was felt 6 cm. below the right costal margin. The temperature, pulse rate, respiration and blood pressure were normal. In view of the history of an attack of pain five years previously, a tentative diagnosis was made of chronic cholecystitis with stone in the common duct. The possibility of an acute atrophy of the liver was



Fig. 2 (case 2).—Diffuse central and midzone necrosis.

considered in view of the history of taking cinchophen, but it was felt that stone in the common duct could not be ruled out.

The results of laboratory tests that were of interest were a positive direct van den Bergh reaction of 14.8 mg. per hundred cubic centimeters and bile in both the urine and the feces. The patient's condition during his stay in the hospital was one of increasing toxemia and progressive jaundice. On August 23, he died in coma, fifteen days after the onset of acute symptoms, and about twelve weeks after the first use of the drug.

Autopsy was performed three hours after death. The body was deeply jaundiced. The liver was found to be the seat of the principal damage, though it was of normal size and weight. It showed on its outer surface small yellowish areas surrounded by reddish-brown, firmer tissue. On section, the yellowish areas appeared to be raised above the general level and had a somewhat granular appearance.

Histologically, the liver showed in every lobule extensive necrosis of the hepatic cells with destruction present throughout, but always greatest about the central veins. The lobules were greatly distorted in size and shape, and many showed complete disorganization. The best preserved hepatic cells were seen in the peripheral zones. Even here, they showed all degrees of degenerative change, with almost none appearing normal. The surviving hepatic cells were arranged in irregular groups in the collapsed reticulum of the lobule. In many instances a pseudotubular arrangement of hepatic cells (like a bile duct) was seen. The hepatic cells in many lobules were completely autolyzed. The remnants of these cells were not observed, the detritus apparently having been rapidly removed by leukocytic action. The cells that remained showed marked granular degeneration



Fig. 3 (case 2).—Surviving liver cells in peripheral zone, showing pseudotubular arrangement. Note the contrast between “pseudotubuli” and intact biliary ductules.

of their cytoplasm and vacuolization by globules of fat and droplets of fluid. The nuclei were often pyknotic, and many were absent. Where the parenchyma had disappeared the stroma remained and had fallen together, giving an impression of fibrosis; but this was only relative, being due to the loss of hepatic tissue. The sinusoids were irregular and were filled with red blood cells. No extravasated blood was noted. The portal sheaths and the structures of the hepatic triads showed no discernible change. In the apparently fibrosed areas, which really represented the collapsed stroma of completely disorganized lobules, there was a moderate infiltration by lymphocytes, plasma cells, polymorphonuclear leukocytes, eosinophils and endothelial cells; but these were not found in numbers approaching

an active inflammatory exudate. Great numbers of phagocytic mononuclear cells were not present.

The findings in the other organs included pulmonary congestion, cloudy swelling of the heart muscle and of the kidneys, and a phlegmonous gastro-enteritis of marked degree. The gastro-intestinal lesion was of particular interest, in view of the recent papers of Churchill and Van Wagoner,<sup>22</sup> in which was reported the production of gastric and duodenal ulcers in association with hepatic degeneration in experimental cinchophen poisoning in dogs. They remarked that gastro-intestinal symptoms were often noted in connection with cinchophen intoxication, though in most clinical pathologic studies gastro-intestinal lesions have not been mentioned, the changes in the liver being generally the center of interest.

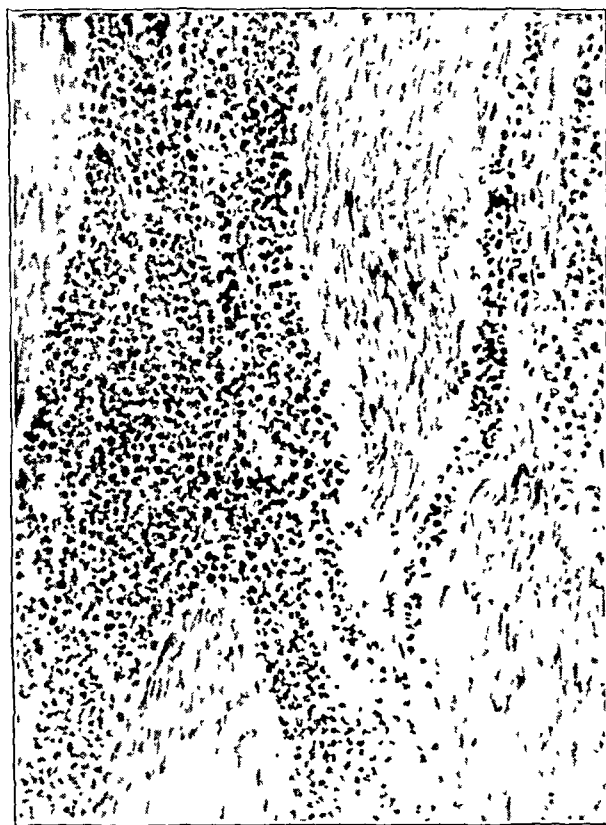


Fig. 4 (case 2).—Diffuse acute cellulitis in the wall of the stomach.

The gross appearance of the stomach and intestinal tract revealed marked jaundice of these structures with congestion of the serosa. The striking lesion was confined to the stomach and duodenum. It was evident on palpation that the wall of the stomach was heavy, soft and boggy. When the stomach and duodenum were laid open, their walls were seen to be greatly thickened by an acute inflammatory reaction accompanied by much edema. The tissues appeared glassy, translucent and turgid with fluid. The gastric mucosa showed intense congestion and superficial necrosis. The wall of the stomach reached a thickness

22. Churchill, T. P., and Van Wagoner, F. H.: Cinchophen Poisoning, *Proc. Soc. Exper. Biol. & Med.* **28**:581, 1931. Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning of Dogs, *Arch. Path.* **14**:860 (Dec.) 1932.

of 2.5 cm. The pylorus was actually closed by the swelling. The mucosa throughout the duodenum was equally engorged, and the ampulla of Vater was swollen and narrowed. The remainder of the intestinal tract showed much less edema and congestion. The mucosa throughout was covered by glairy, bile-stained mucus.

Microscopic examination revealed a diffuse acute phlegmonous inflammation of the walls of the stomach and duodenum. The mucosal epithelium was in an actively functioning state. The superficial lesions were slight and consisted of erosions rather than true ulcerations. In all the remaining coats of the gastric and duodenal walls, however, there was an extreme degree of loosening of the tissues by inflammatory edema and a cellular exudate made up almost completely of polymorphonuclear leukocytes. True necrosis and abscess formation were lacking. Vascular lesions were not evident. The picture was that of an acute diffuse cellulitis. No bacteriologic studies were made at autopsy, but Gram-Weigert stains of sections of the wall of the stomach showed vast numbers of gram-positive cocci in pairs and short chains lying in and between the polymorphonuclear leukocytes of the exudate. The organisms were evidently streptococci, and this is the organism usually associated with this form of gastro-enteritis.

#### COMMENT

From the literature on cinchophen intoxication, it appears that the hepatic lesion is essentially identical with the acute and subacute atrophies of the liver produced by a variety of known poisons, among which trinitrotoluene as described by Haythorn<sup>5</sup> is a good example. However, the terminology employed in a number of the reports on cinchophen poisoning has confused the lesions it produces in the liver with those of true idiopathic yellow atrophy. Marchand<sup>23</sup> pointed out in 1895 that yellow atrophy showed two stages, an acutely fatal stage with degeneration and a subacute to chronic stage with regeneration of large nodular masses of hepatic parenchyma alternating with bands of fibrosis. In 1911, Mallory<sup>24</sup> designated the end-result of yellow atrophy as toxic cirrhosis and emphasized the pathogenic relationship of the acute stage to the fibrosed and nodular healed stage.

In 1927, Wilson and Goodpasture<sup>25</sup> reported a series of cases of yellow atrophy illustrating the hepatic lesions in the acute, subacute and chronic stages. They stressed the view that a variety of toxic degenerations of the liver of known cause are now recognized, and emphasized the importance of distinguishing these from the idiopathic form. Further, they showed that true yellow atrophy tends to produce focal lesions, while the toxic degenerations of known cause are diffuse. This fact, they believed, makes it possible to distinguish the more

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23. Marchand, F.: Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasie, Beitr. z. path. Anat. u. z. allg. Path. **17**:206, 1895.

24. Mallory, F. B.: Cirrhosis of the Liver. Five Different Types of Lesions from Which It May Arise, Bull. Johns Hopkins Hosp. **22**:69, 1911.

25. Wilson, J. D., and Goodpasture, E. W.: Yellow Atrophy of the Liver: Acute, Subacute and Healed, Arch. Int. Med. **40**:377 (Sept.) 1927.

coarsely lobulated healed stage of yellow atrophy from the fine diffuse fibrosis of healed toxic degeneration of known cause. For these reasons they proposed to confine the use of the terms acute, subacute and healed yellow atrophy to the stages of the idiopathic form, the atrophies of the liver of known cause to be designated by the acting poison in each case.

Beaver and Robertson,<sup>21</sup> in their recent paper, carefully avoided confusion by referring to the hepatic lesions as "acute atrophy with diffuse acute parenchymatous degeneration and necrosis, due to cinchophen." They did not use the term yellow atrophy. We believe this is an important distinction, as it avoids grouping all atrophies of the liver without regard to their causes.

One feature which sets cinchophen apart from other etiologic agents causing toxic degeneration of the liver is the evident retardation of parenchymatous regeneration. Why this is so has not been explained; the inhibition may be due to persistent action of the drug or to factors as yet unknown. Further, true fibroblastic proliferation is virtually absent in the earlier stages of the healing process. The end-result in patients who survive the acute and subacute stages is probably a type of diffuse cirrhosis; but as there are reports of complete clinical recovery from cinchophen poisoning, it may be that practically complete restitution of the liver is possible. The facts regarding these points will be determined only when patients are brought to autopsy months or years after recovery from cinchophen poisoning.

The features distinguishing the lesion of cinchophen poisoning from that of idiopathic yellow atrophy were well demonstrated in the two cases reported in this paper. In the first, the lesion in the liver was essentially one of parenchymatous degeneration without evident loss of hepatic cell substance and hence with well preserved hepatic architecture. It was a degeneration due to cinchophen in an earlier stage than any so far described. The embalming process and the postmortem period have to be considered in studying this tissue, but it seems certain that the outstanding characteristic was the presence of extreme degeneration without actual dissolution of the hepatic cells. Why the disintegrative process was delayed in this case is not clear; the liver might have been somewhat protected by the therapeutic measures instituted one week after the onset of symptoms. The lack of dissolution seen microscopically casts some doubt on the report that this liver was reduced in size. In early cinchophen poisoning the liver is generally found enlarged, and in this case the lack of disorganization and dissolution of the lobules would indicate that the tissue had come from a liver of at least normal size.

The second case is clearcut and typical of cinchophen poisoning. The liver illustrates the histologic changes which have been interpreted by some observers as fibrosis and the formation of new bile ducts, but

which Beaver and Robertson have shown to be collapse of hepatic stroma, instead of fibrosis, and surviving and regenerating columns of hepatic cells (or pseudotubuli), instead of newly formed bile ducts. Regarding the phlegmonous gastro-enteritis, this type of lesion is always associated with ulceration or at least with some break in the surface of the gastric mucosa. In this case, nothing was found except erosions that may well have been simply postmortem degeneration, so that the relation of the infection to a possible local irritant action of the drug, and even the mode of entrance of the infection, must remain obscure.

#### SUMMARY

Two cases of cinchophen poisoning are presented with the observations at autopsy. Both cases illustrate marked toxic degeneration of the liver. In the first case an early stage of the process is shown, which is the more interesting since the picture is not the usual one seen at autopsy. We believe it represents an earlier stage than has been previously reported. In the second case, the lesions of the liver, as well as of the heart muscle, kidneys and gastro-intestinal tract, are typical and have been noted by others.

#### CONCLUSIONS

1. Cinchophen intoxication causes a type of hepatic damage which is essentially like the acute and subacute atrophies of the liver due to other known toxic agents. It is a uniformly diffuse lesion, involving primarily the central zones of the lobules. Its intensity varies in different lobules. It is properly termed an acute or subacute toxic (cinchophen) degeneration and atrophy.
2. This toxic atrophy of the liver, if not fatal, is probably followed by some regeneration of the parenchymal cells, and may lead to a diffuse cirrhosis.
3. An acute gastro-intestinal lesion of a severe type may accompany the toxic degeneration of the liver.

# FATTY INFILTRATION OF THE MYOCARDIUM

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Some clinically recognized disorders the cause or causes of which cannot be demonstrated by gross or microscopic anatomic changes are explained today on a functional or a pathologicophysiologic basis. For example, death is occasionally believed to be due to spasm of the coronary arteries, ventricular fibrillation, shock, or other functional disturbance. While undoubtedly fatal conditions are encountered for which a satisfactory explanation cannot be obtained by the use of present morphologic methods, it must be emphasized that such assumptions should be made only after careful study has ruled out the possibility of a morphologic explanation.

After analysis of a series of cases of fatty infiltration of the myocardium, it became evident that this myocardial lesion had caused a number of deaths which could not be explained clinically on a morphologic basis and therefore had been attributed to functional disorders. In other words, as a result of our studies, fatty infiltration of the myocardium was shown to be an easily demonstrable and plausible morphologic cause of otherwise unexplained sudden myocardial insufficiency and death.

Fatty infiltration of the myocardium was a more conspicuous clinical and pathologic diagnosis a few decades ago than it is today. Modern clinicians mention this condition among cardiac disturbances, but are very cautious in their interpretation of its significance. Perhaps the fact that the clinical manifestations are so indefinite has relegated this disease entity to an obscure place in considerations of cardiopathy. We find fatty infiltration of the myocardium, fatty heart, lipomatosis cordis and cor adiposum listed in current clinical textbooks, but these diagnoses appear infrequently on clinical charts. The pathologists are as loath as the internists to consider the condition as the cause of death, and mention of it forms a mere appendage to the anatomic diagnosis.

In routine postmortem examinations we found fatty infiltration of the myocardium in a sufficient variety of cases to stimulate our

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interest in its possible significance. By fatty infiltration of the myocardium is meant the formation of an abundance of subepicardial fat which extends into the myocardium and occupies the usual position of the muscle fibers. This apparently has nothing in common with fatty degeneration, often associated with infectious diseases or sometimes a result of dyscrasias of the blood or of chronic passive hyperemia. Fatty degeneration is a deteriorative process in the course of which fat becomes apparent in the cells, while fatty infiltration affects cells which normally contain fat and represents an alteration simply of the normal fat depots and transport (Karsner). The two conditions are often discussed under the same heading, and in reviewing the literature we occasionally had difficulty in determining to which an author referred. In this communication only fatty infiltration will be discussed.

#### LITERATURE

Because we were unable to find a compilation of the literature on this subject, we thought it of interest to cite the more important view expressed.

Corvisart, in 1818, admitted the possibility of fatalities due to fatty infiltration but had never observed any. He cited three fatal cases described by Kerckring, Bonnet and Morgagni respectively.

Leyden, in 1882, stated that fatty heart and fatty degeneration have nothing in common, and that death in some patients can be explained by fatty infiltration of the heart (fatty heart).

Hamilton, in 1889, considered that atrophy of muscle fibers associated with fatty infiltration precedes the infiltration instead of being the result of mechanical pressure of the fat on the muscle. He referred to cases recorded by Fothergill and by Leyden in which fat had accumulated to the extent of interfering with the motion of the heart.

Brouardel, in 1895, stated that a relatively unimportant lesion such as fatty infiltration may be quiescent throughout life and be revealed only on the occasion of accessory circumstances. A patient may die unexpectedly as a result of this condition.

Pepper, in 1896, stated that often, in cases of fatty infiltration, the heart muscle is healthy, but that more often, in cases of considerable deposit of fat, the fibers undergo atrophy and degenerative changes from pressure. The myocardium may be reduced to a narrow rim. The cavity is dilated, and rupture of the heart is not uncommon. There is frequently a hereditary tendency, but overeating, excessive drinking of alcoholic beverages and sedentary habits are powerful determining factors. There is, however, a form of fatty infiltration in emaciation, in atrophy of old age and in cachexia.



Hasenfeld and Fenyvessy, in 1899, did not believe that a fatty heart could be diagnosed clinically. Animals which were poisoned with phosphorus showed no evidence of cardiac decompensation until shortly before death.

Rosenbach, in 1899, mentioned that a nutritional disturbance causes muscular atrophy of the heart and secondary replacement with fat.

Hirsch, in 1901, recommended the term "heart trouble in obese patients" rather than "fatty heart."

Schluter, in 1906, made the following statement:

The fat infiltration in the near vicinity and within old myocardial scars was conspicuous. Fat infiltration, increase in connective tissue, the disappearance of the parenchyma and lymphocytic infiltrations are the result but not the causes of gradually occurring insufficiency of the myocardium.

Fisher, in 1908, stated:

Some text books seem to indicate and the records of published cases of death make it clear that excess of fat covering the heart and existing in the interstitial structures within the heart wall is often considered to be an evidence of cardiac weakness. There is, I believe, no evidence in favour of such view. . . . Dyspnea, if present, must have been due to work entailed in moving an unusually heavy body. . . . The fat going between the muscle fibers may occasionally be very great in amount, yet the muscle fibers prove on microscopic examination to be quite healthy.

Kisch, in 1908, remarked that any factor which raises the blood pressure and which under normal conditions is not harmful may cause sudden death of patients with a fatty heart.

Powell, in 1909, attributed certain varieties of fatty heart to alcohol. He described two varieties: one in which fat encroaching on muscle fibers may cause their atrophy and replacement, and one in which fat fills up the interstices left by the atrophy of muscles. The first variety is the most common, and is encountered in inactive, middle-aged persons with good appetite and digestion but poor assimilation. These patients, while in a far less dangerous condition than those suffering from fatty degeneration, are liable to succumb to acute illnesses of any kind, particularly to bronchitis, pneumonia, typhoid and surgical injury.

Osler, in 1910, stated that fatty infiltration is ususally a simple excess of normal subepicardial fat which forms a part of general obesity. When pronounced it may lead to dangerous or even fatal impairment of the contractile power of the heart.

Sahli, in 1911, remarked that pronounced slowing of the heart rate to as low as 20 beats per minute is observed in fatty infiltration.

Kolisko, in 1913, considered that fatty infiltration can probably cause functional disorders of the heart, but that only in the absence of any other pathologic changes at autopsy may death be attributed to this condition.

Wegelin, in 1913, stated that fatty infiltration of the myocardium may cause sudden death. He recommended strict differentiation between fatty infiltration and fatty degeneration.

Eyselein, in 1914, mentioned two patients with marked fatty infiltration of the myocardium who died suddenly. He also stated that fatty hearts are found frequently, in about 25 per cent of all cases, but are rarely recognized clinically.

Aschoff, in 1919, stated that in cases of generalized adiposity the relatively small heart works under a greater strain and therefore may easily become incompetent. Fatty infiltration of the myocardium *per se* seems less likely to be the cause of insufficiency of the heart.

Henry and Smith, in 1919, held that fatty infiltration occurs frequently and that its presence should be suspected during life in patients with cardiac disease who exhibit a general tendency to obesity.

Pupko, in 1921, remarked that a slight fatty change in the heart may be physiologic.

Kratter, in 1921, stated that a fatty heart may lead to sudden death, especially on occasions of muscular overactivity, overfilling of the stomach, psychic excitement and defecation. A fatty heart is found in almost all drunkards.

Kaufmann, in 1922, distinguished between fatty degeneration and fatty infiltration of the myocardium. He stated that in the latter condition the heart may be enlarged, if the patient is obese but muscular, or atrophic in obese but myasthenic patients and in persons with marked cachexia. Fatty infiltration of the myocardium may lead to unexpected death on any occasion demanding increased cardiac activity. Also, rupture of such a heart may occur if the myocardium is atrophic or the seat of fatty degeneration.

Vaquet, in 1924, considered that uncomplicated fatty infiltration cannot cause death. Nevertheless, the rôle of cardiac adiposis is not negligible. It is certain that a luxurious infiltration of fat into the subepicardial and intramyocardial spaces has an unfavorable influence on cardiovascular lesions, notably on myocardial sclerosis. In this event, the fibers, in which nutrition is impaired, are prone to rupture more easily. Vaquet also quoted Gallaverdin, who distinguished three forms of fatty infiltration of the heart, a benign form with indefinite symptoms, an intermediate form with cardiac asthenia, and a severe form with angina pectoris, acute edema of the lungs, crises of heart failure or of uremia.

Mönckeberg, in 1924, discussed this subject extensively. He also referred to fatty infiltration of the conducting system and reviewed the literature.

Karsner, in 1926, held that functional disturbances depend largely on the degree of infiltration, and that it is possible that in excessive infiltration with fat the function of the heart may be disturbed. But it is also possible that these disturbances are due rather to atrophy of muscles. Ordinary degrees of fatty infiltration apparently have no influence on cardiac activity.

French, in 1928, listed fatty infiltration of the heart among the causes of failure of the right side of the heart.

Hewlitt, in 1928, stated that in obese persons the heart, like the voluntary muscle, becomes small and weak owing to lack of exercise. Its strength is further diminished by fatty deposits about the myocardium.

Norris and Landis, in 1929, stated that in obese persons with fatty infiltration of the heart, dyspneic attacks resembling asthma are not uncommon. These are usually ascribed to obesity but more often are an evidence of cardiac weakness.

Zarday, in 1930, remarked that an examination of one hundred and sixty adipose persons revealed, in 90 per cent, objective disturbances of the circulation as found by determination of the pulse rate, arterial and venous pressure, vital capacity, etc.

White, in 1931, considered the clinical significance of *cor adiposum* obscure. "The truth probably lies between the two extremes, that the fatty heart is a common and dangerous condition and that it does not exist at all."

#### MATERIAL AND METHODS

During routine autopsies we found a large number of hearts infiltrated by fat. The study here presented deals with the examination of fifty-eight hearts, all of which both grossly and histologically showed fatty infiltration. Twenty-eight were carefully examined histologically. Many sections were taken from the ventricles and occasionally from the auricles; sudan III and osmic acid were used to demonstrate the presence of fat. In the other thirty-two hearts, the sections taken as a routine at autopsy and stained with hematoxylin and eosin were used. Hearts which showed definite valvular defects were not included.

After examination of the hearts, we studied the clinical records of the fifty-eight patients with the purpose of correlating fatty infiltration of the myocardium with the clinical picture and of evaluating this finding as a cause of death.

#### RESULTS

*Pathologic Observations.*—The hearts weighed from 200 to 800 Gm., the majority weighing between 300 and 400 Gm. The site of the most extensive involvement by fat was uniformly the right ventricle. The fat seemed to follow directly the course of the coronary vessels. Section showed that it apparently had infiltrated the myocardium, most commonly the lateral wall of the right ventricle, corre-

sponding to the line of cut surface made for opening the tricuspid valve. The extension of the fatty tissue into the myocardium varied from a moderate infiltration involving only the layers adjacent to the epicardium to a replacement of the entire thickness. This severe infiltration was observed only in the region of the right ventricle. In several hearts fat was likewise observed in the left ventricle and in the right auricle. In a few instances it was noted in the subendocardial layers of the left ventricle.

Corresponding to the degree of infiltration recognized grossly, a varying amount of fat was found in histologic sections. Invariably,

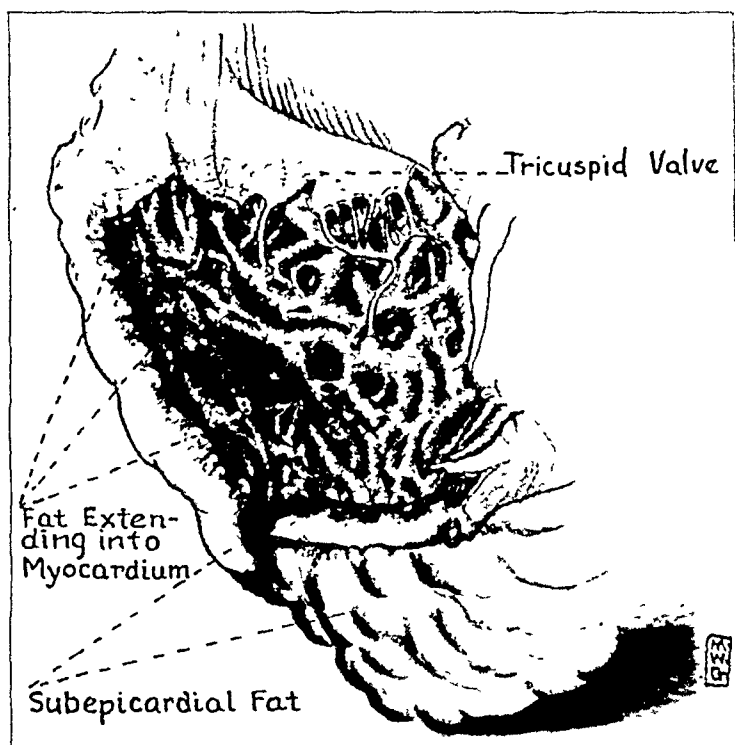


Fig. 1.—Drawing of the right ventricle showing the site of predilection of fatty infiltration.

the right ventricular wall showed the fat to a much greater extent than the left. In cases of slight involvement, the usual sharp line of demarcation between the subepicardial fatty tissue and the myocardium was indistinct, and only the outer layers of the myocardium were replaced by fat. Some of the sections showed the extension of fat into the myocardium, following the interstitial spaces and separating muscle fibers into groups which gave a fanlike appearance. In early cases, fat could be demonstrated in the interstitial spaces and perivascular regions, apparently some distance from the subepicardial fatty tissue and not continuous with it. The muscle fibers between the deposits of fatty tissue were atrophic; their cytoplasm was granular in appearance, and in many instances the nuclei were not visible. In other

portions only remnants of muscle fibers were noticeable, and in still other areas fat completely replaced the muscle fibers. Many of these sections, however, still revealed apparently normal blood vessels. In many microscopic fields of sections taken from severely infiltrated hearts the fatty tissue penetrated the entire thickness of the myocardium and appeared just beneath the endocardium. The location of the fatty tissue was recognized as abnormal because of its proximity to the endocardium. Morphologically the fat in these sections was similar to that of other fatty tissues. Sections taken from the left ventricle



Fig. 2.—Fatty infiltration of the myocardium. Note extension of the subepicardial fat tissue into the myocardium. (Photograph of heart shown in figure 1.)

showed much less severe changes. Here too the layers of the myocardium closest to the epicardium were primarily involved. The more severe cases showed extension of fat deep into the muscle layer and islands of fat cells in the interstitial spaces, discontinuous with the subepicardial fat. The preservation of the blood vessels was noticeable in these sections. In a few instances, fat was found in the subendocardial layer of the interventricular septum close to and also within the bundle of His. In none of our cases, however, could we demonstrate replacement of the entire thickness of the wall of the left ventricle, as in the right ventricle. None of the sections showed evidence of

inflammatory cells or of new formation of blood vessels indicating the organization of an inflammatory exudate.

The gross and histologic changes gave the impression that the subepicardial fatty tissue had, like a malignant tumor, invaded the myocardium and replaced the muscle fibers. In the sections the fat followed the perivascular spaces into the myocardium. It is possible



Fig. 3.—The appearance of fat in the wall of the left ventricle. Note the perivascular distribution of the fat. Sudan III-Boehmer's hematoxylin stain;  $\times 150$ .

that the subepicardial fatty tissue primarily proliferates and secondarily causes atrophy of the muscle fibers by pressure; but it is more likely, as Mönckeberg stated, that there is a transformation of the interstitial tissue into fatty tissue. The presence of islands of fat cells in the myocardium at a distance from the subepicardial fat and not continuous with it may support this theory. Because in many

instances the heart was larger than normal it is not likely that the increase in fat in these cases constituted a replacement or "filling in" phenomenon, as stated by older authors. It seems more likely that the increased fat had produced secondary atrophy, probably by pressure. Even in the cases in which the heart was obviously hyper-



Fig. 4.—Section of the wall of the right ventricle. Note the atrophy of the muscle fibers, their fanlike appearance and the "burrowing in" of the fat tissue. Hematoxylin-eosin stain;  $\times 175$ .

trophic, the remnants of muscle fibers found surrounded by fat were definitely atrophic. The atrophy and disappearance of the muscle fibers were probably not the result of a nutritional disturbance in view of the presence of open blood vessels within the newly formed fatty tissue. The lack of any inflammatory reaction is interesting and may indicate

autolysis of the muscle fibers. In other words, it is probable that the muscle fibers had not been broken down and carried away by phagocytic cells but had been autolyzed.

In our series we did not encounter the extreme fatty infiltration that leads to rupture of the heart and hematopericardium, but there are a few references in the literature to such an occurrence. Pepper stated

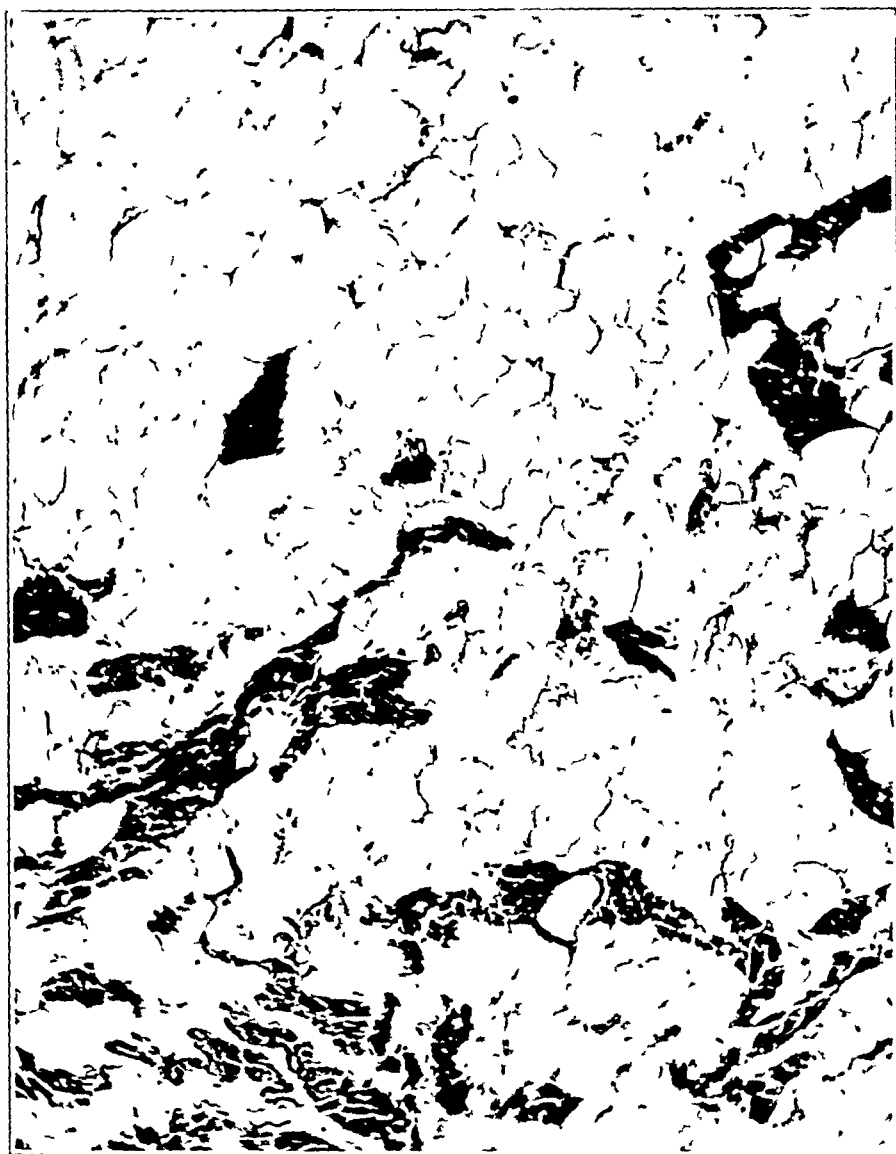


Fig. 5.—Almost complete replacement of the myocardium by fat tissue. Hematoxylin-eosin stain;  $\times 225$ .

that rupture of the heart is not uncommon as a result of fatty infiltration, and Vaquez suggested its possibility. Krumbhaar and Crowell, however, in reviewing the literature on rupture of the heart, repudiated fatty degeneration and fatty infiltration as etiologic factors, ascribing the rupture in hearts showing fatty conditions to coronary changes and myocardial infarcts. They described as a striking feature the excessive



amount of subepicardial fat noted in fifty-eight cases. They considered the frequent occurrence of marked fatty deposits in the myocardium to be curious and of obscure significance. Locke, who described a case of rupture of the right ventricle, mentioned the presence of a large amount of fat in the heart. Mönckeberg mentioned cases of rupture of the heart as a result of fatty infiltration described by Weiland and by Draeck, and discussed the occurrence of this condition. Also, Rintelen very recently referred to a case of rupture of a fatty heart. The occurrence of rupture speaks without doubt for the severity of the fatty infiltration.

*Etiology.*—As to the etiology of fatty infiltration of the myocardium, we have very little to state. In cases of general obesity, the heart may easily show an increase of subepicardial fat tissue and extension of this tissue into the myocardium. A few of the patients in our series gave clinical evidence of diabetes mellitus, which may or may not cause one to regard fatty infiltration as the result of faulty metabolism. Powell stated that primary fatty infiltration is met with in inactive, often self-indulgent persons—middle-aged men and women near the climacteric. People with good appetite and good primary digestion but with faulty assimilation and inadequate eliminative power are subject to this disease. Indulgence in alcoholic drinks, such as malt liquors and sweet wines, favors its occurrence. In one of our patients whose history indicated excessive use of alcohol autopsy revealed atrophic cirrhosis of the liver. It is possible that alcohol in this case was the direct cause of fatty infiltration. We shall not discuss whether so-called “beer drinker’s heart” is fatty infiltration of the myocardium or a hypertrophic heart, the result of overwork due to the excessive ingestion of alcoholic beverages. The heart in the case just mentioned was somewhat hypertrophic (weight, 400 Gm.). The right ventricle was markedly dilated, its wall largely made up of fat.

#### CLINICAL CORRELATION

We have attempted to divide our fifty-eight cases into three main groups.<sup>1</sup> Group I comprises those in which fatty infiltration of the myocardium was the only obvious cause of death (two cases). In group II we placed the cases in which fatty infiltration of the myocardium was apparently a contributory factor in the cause of death (twenty-nine cases). Group III is made up of cases in which fatty infiltration of the myocardium was an incidental finding (twenty-five cases). There were two cases which could not be classified in any of the three groups, and these will be considered separately. The groups are presented in the accompanying tables.

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1. The Medical Department of the Michael Reese Hospital supplied the clinical data.

Group I is the most interesting because fatty infiltration of the myocardium has been considered the primary cause of death. In the first case, the patient was an obese woman, aged 49, who died suddenly nine days after an operation on the knee joint. There was no clinical evidence of previous heart failure. At autopsy there were marked fatty infiltration of the heart and chronic passive hyperemia of the lungs. A careful search of all organs, including the brain, revealed no other abnormalities. In the second case, the patient was also a 49 year old woman, whose condition was diagnosed clinically as cardiac decompensation due to fatty heart. At autopsy, after a careful study of all organs, no anatomic changes were found other than those of the heart.

These two cases are significant, especially the second, which clinically showed evidence of cardiac decompensation. We shall refer to this case later. The question may be raised as to whether or not death might have been caused by some other condition which could not be demon-

TABLE 1.—*Group I: Cases in Which Fatty Infiltration of the Myocardium Was the Only Abnormality Found at Autopsy*

Case	Age	Sex	Nutrition	Clinical Notes	Pathologic Notes
1	49	F	Obese	Prepatellar bursitis; sudden death	Fatty infiltration of myocardium; no changes in the brain
2	49	F	Obese	Weakness, precordial pain and dyspnea for 5 years; râles at both bases; arrhythmia; sudden death	Fatty infiltration of myocardium

strated at autopsy, such as spasm of the coronary arteries, minute changes in the medulla oblongata, sudden insufficiency of glands of internal secretion without noticeable anatomic lesions or poisoning. The history of these patients did not reveal any attacks of cardiac disturbance referable to coronary spasm, and there was nothing in the history or anatomic findings suggestive of poisoning. Because of the extent of the fatty infiltration, because of the absence of other pathologic findings and in an effort to associate obvious pathologic conditions with causes of death, we must hold fatty infiltration of the myocardium responsible for the death of these patients.

In the second group of cases, numbering 28, fatty infiltration of the myocardium probably played a contributory rôle in causing death. In this group some of the patients at autopsy showed marked pathologic lesions, such as diffuse carcinomatosis, pneumonia and small pulmonary emboli. Though these changes in some instances were very severe and probably sufficient per se to explain death, had death occurred at a subsequent time, it is likely that the fatty infiltration of the myocardium played a contributory rôle in causing the untimely death. There are also several patients in this group who died suddenly in whom autopsy

TABLE 2.—*Group II: Cases in Which Fatty Infiltration of the Myocardium Was Apparently a Contributory Cause of Death*

Case	Age	Sex	Nutrition	Clinical Notes	Pathologic Notes
3	55	F	Under-nourished	Sudden death 1 week after nephrectomy	Bronchopneumonia; local peritonitis and cystitis; fatty infiltration of myocardium
4	52	F	Obese	Death 3 days after onset of respiratory symptoms	Bronchopneumonia; fatty infiltration of myocardium
5	77	M	Well nourished	Gradual death 6 days after cystostomy	Early bronchopneumonia; edema and chronic passive hyperemia of lungs; cystitis and bronchopneumonia; fatty infiltration of myocardium
6	56	F	Well nourished	Gradual death 8 days after entero-enterostomy	Bronchopneumonia; old peritonitis; fatty infiltration of myocardium
7	68	F	Obese	Gradual death	Chronic bronchitis; emphysema of both lungs; fatty infiltration of myocardium
8	63	F	Well nourished	Gradual death 6 weeks after removal of half of nose for carcinoma	Bilateral bronchopneumonia; chronic leptomeningitis; fatty infiltration of myocardium
9	50	M	Under-nourished	Death 4 hours after incision of psoas abscess; diagnosis "shock"	Chronic pulmonary tuberculosis; fatty infiltration of myocardium
10	77	F	Obese	Gradual death; acute suppurative parotitis; bronchopneumonia (lower lobe of left lung)	Acute suppurative parotitis; bronchopneumonia (lower lobe of left lung); edema of lungs; fatty infiltration of myocardium
11	36	M	Well nourished	Found dead in bed 24 hours after incision of peritonsillar abscess	Acute ulcerative tonsillitis; pulmonary edema; bronchopneumonia; fatty infiltration of myocardium
12	66	M	Well nourished	Sudden death 1 day after incision of left and right pectoral muscles; carcinoma of larynx	Bronchopneumonia with gangrene; recent tracheotomy for carcinoma of larynx; fatty infiltration of myocardium
13	45	F	Obese	Gradual death after febrile course; evidence of circulatory collapse	Chronic fibrocaceous tuberculosis of lungs, liver and spleen; fatty infiltration of myocardium
14	58	M	Under-nourished	Death 5 days after thyroidectomy	Bronchopneumonia; fatty infiltration of myocardium
15	24	F	Under-nourished	Death 28 hours after thyroidectomy	Bilateral chronic caseous tuberculosis; fatty infiltration of myocardium
16	25	F	Well nourished	Sudden death 1 month post partum and 4 days after incision of leg	Embolus in branch of pulmonary artery; thrombophlebitis; fatty infiltration of myocardium
17	52	F	Under-nourished	Death 30 hours after removal of both ovaries; diagnosis "shock"	Diffuse metastases of papilliferous carcinoma of ovary; embolus in branch of pulmonary artery; fatty infiltration of myocardium
18	47	F	Well nourished	Death 4 days after drainage of perinephric abscess	Carcinoma of suprarenals; small pulmonary emboli; fatty infiltration of myocardium
19	62	M	Well nourished	Sudden death 2 days after prostatectomy	Pulmonary emboli; fatty infiltration of myocardium
20	67	M	Obese	Cardiac decompensation	Multiple emboli in small branches of pulmonary arteries; coronary sclerosis; fatty infiltration of myocardium
21	75	F	Well nourished	Gradual death 4 days after onset of respiratory symptoms; chronically ill 5 years	Coronary sclerosis and thrombosis (anterior descending branch); bronchopneumonia; fatty infiltration of myocardium

TABLE 2.—*Group II: Cases in Which Fatty Infiltration of the Myocardium Was Apparently a Contributory Cause of Death—Continued*

Case	Age	Sex	Nutrition	Clinical Notes	Pathologic Notes
22	69	F	Obese	Diabetes mellitus	Generalized arteriosclerosis with coronary sclerosis; fatty infiltration of the myocardium
23	72	F	Obese	Death 24 hours after operation for prolapse of uterus; death considered due to thyroid crisis	Generalized arteriosclerosis with coronary sclerosis; bronchopneumonia; fatty infiltration of myocardium
24	62	M	Obese	Death following coma of 2 days' duration	Generalized arteriosclerosis with coronary sclerosis; bronchopneumonia; myocardial fibrosis; fatty infiltration of myocardium
25	44	F	Well nourished	Gradual death; carcinoma of the sigmoid	Carcinoma of the sigmoid with metastases to lungs, pleurae and liver; fatty infiltration of the myocardium
26	56	F	Well nourished	Gradual death 4 months after bilateral mastectomy	Recurrent adenocarcinoma of breast with metastases to lungs, liver and vertebrae; fatty infiltration of myocardium
27	44	M	Emaciated	Sudden death 3½ months after closure of colostomy wound	Ulcerating adenocarcinoma of rectum with peritoneal metastases; fatty infiltration of myocardium
28	55	F	Well nourished	Gradual death 14 days after exploratory laparotomy	Papillary carcinoma of ovary with peritoneal metastases; edema and hyperemia of lungs; fatty infiltration of myocardium
29	45	F	Emaciated	Carcinoma of sigmoid; gradual death	Adenocarcinoma of sigmoid with generalized peritoneal metastases; bronchopneumonia; fatty infiltration of myocardium
30	38	F	Obese	Gradual death; cirrhosis of liver	Atrophic cirrhosis of liver; myocardial fibrosis; fatty infiltration of myocardium
31	57	M	Well nourished	Gradual death; hypertension; intraventricular block of bundle branch type	Nephrosclerosis of arteriolar variety; hypertrophy of heart; fatty infiltration of myocardium with involvement of bundle of His

revealed moderate bronchopneumonia or small pulmonary emboli. Probably a normal heart could have responded to the greater demand imposed on it by either of these conditions. However, a heart infiltrated by fat, especially when the infiltrate involves mainly the myocardium of the right ventricle, apparently does not always possess the reserve power to overcome the greater demand and may therefore fail suddenly. We believe that in some of these patients, fatty infiltration of the myocardium hastened, if it did not cause, death.

Case 31 (table 2) is noteworthy. The clinical diagnosis was arterial hypertension and hypertrophy of the heart. Before the patient died, the diagnosis of intraventricular block of the bundle branch type was made from the electrocardiogram. At autopsy there were a nephrosclerosis of the arteriolar variety, hypertrophy of the heart and marked fatty infiltration of the myocardium. The fat was found grossly also in the interventricular wall of the left ventricle just beneath the endo-

cardium in the region of the bundle of His. Histologically, atrophy of the fibers and interruption of the bundle by fat could be made out in one place.

An interesting group of cases consists of those in which death occurred during or after anesthesia, either general or spinal. For convenience these are assembled in group II and in an unclassified group because we have no absolute proof that fatty infiltration of the myocardium was the sole cause of death. Clinically, a so-called "reflex death" was sometimes thought to have occurred. At autopsy such a condition, of course, could not be proved, but neither could it be disproved. The fatty infiltration of the heart, however, was so severe that, from the point of view of the pathologist, it could have been the cause of death.

TABLE 3.—*Group III: Cases in Which Fatty Infiltration of the Myocardium Was an Incidental Finding*

The 25 cases (cases 32 to 56) in this group are classified as follows:		Number of Cases
Nutrition:		
Obese .....		6
Well nourished .....		10
Emaciated .....		9
Chronic diseases .....		10
Acute diseases .....		15

The third group is largely of statistical interest since we were unable to correlate fatty infiltration of the myocardium with death. The infiltration was coincidental with various types of lesions.

The second group and also the third reveal that fatty infiltration of the myocardium may occur without relationship to general nutrition. It may be found in patients suffering from chronic wasting diseases which have led to marked generalized emaciation but may likewise be present in the well nourished and frequently in the obese.

There are two cases in our series which we did not want to classify as belonging to any one of the three groups. The first was that of a boy 12 years old. The clinical and pathologic diagnosis was pseudo-hypertrophic muscular dystrophy. At autopsy there was a marked increase of fat throughout the body with replacement of skeletal muscle tissue by fatty tissue and diffuse fatty infiltration of the myocardium. In addition, bronchopneumonia was found at autopsy, which prevented the inclusion of this case in group I. The bronchopneumonia, however, was neither diffuse nor severe but localized in one portion of a lower lobe. An unchanged heart in a boy 12 years old surely would have responded normally to the slightly increased demand caused by the bronchopneumonia. We believe that the fatty infiltration of the myo-

cardium was part of the general replacement of the muscle tissue by fat and the direct cause of death.

The second case was that of a patient who died after thyroidectomy. The clinical diagnosis was "thyroid crisis." Autopsy revealed hypertrophy and dilatation of the heart and fatty infiltration of the myocardium. We did not classify this case as belonging to group I which consists of cases in which death was a direct result of fatty infiltration of the myocardium because, despite the objective evidence, a functional cause of death could not be disproved clinically. From the point of view of the pathologist, however, who cannot demonstrate thyrotoxicosis at autopsy but who is impressed with the gross and microscopic picture of fatty infiltration of the heart and who sees the disappearance of muscle fibers and their replacement by fat, this case should be considered as one of death from fatty heart.

TABLE 4.—*Unclassified Cases*

Case	Age	Sex	Nutrition	Clinical Notes	Pathologic Notes
57	12	M	Obese	Gradual death; bronchopneumonia; pseudohypertrophic muscular dystrophy	Pseudohypertrophic muscular dystrophy; fatty infiltration of myocardium; broncho- pneumonia
58	52	F	Well nourished	Sudden death 24 hours after thyroidectomy; clinical diagnosis "thyroid crisis"	Fatty infiltration of myo- cardium

Little can be said as to the clinical signs and symptoms of fatty infiltration, and this is probably the reason that this diagnosis has fallen into discredit among clinicians. Brouardel remarked: "The individual with excess fat of the heart is not considered ill. He is of healthy appearance, perhaps a bit short of breath, but never extremely dyspneic. On auscultation one finds no definite signs. The physician states that the heart is a little large, that the tones are a bit feeble, that the impulse is slightly reduced in strength. He cannot make an exact diagnosis; meanwhile, the patient has an affection which exposes him to sudden death." As Ribbert has said, even marked infiltration of fat may show no clinical symptoms. The condition was diagnosed clinically in only one case in our series. This diagnosis (case 2, group I), which was made by a junior intern, was based on the general obesity and the finding of edema of the lungs and ankles. The heart was regular but rapid; the left border was 16.5 cm., and the right border 5 cm., from the mid-sternal line. There were no murmurs or accentuated sounds. Later, arrhythmia was noted, and only one tone, pounding in nature, was heard at the apex. The blood pressure was 126 systolic and 76 diastolic. There was tenderness in the region of the liver, but the organ was not palpable. The patient died suddenly.

The most characteristic feature of such cases is, as a rule, the absence of a history of heart failure and of definite clinical findings indicating chronic passive hyperemia. Apparently, a myocardium which is the seat of fatty infiltration may carry on its function as well as a normal heart, but has no reserve power. This was recognized by Külbs, who stated that it is of practical importance that clinical signs of a failing heart in cases of fatty infiltration of the myocardium may appear suddenly following psychic excitement, operation or physical exertion. We also believe that it is important to realize that a patient with fatty infiltration of the myocardium may be in apparently perfect health but that his heart may fail suddenly, without premonitory symptoms, as a result of insignificant causes. In other words, unexpected death due to fatty infiltration of the myocardium, in our opinion, often can be regarded as an example of sudden death from "natural causes" in the sense of Kolisko.

Fatty infiltration largely involves the right ventricle. Its clinical manifestations are those of failure of the right side of the heart; they are not sufficiently specific to warrant a definite diagnosis. The use of modern methods of recording auscultatory phenomena may reveal some typical changes; likewise, if numerous electrocardiograms are recorded it may be possible to link to fatty infiltration a low voltage or other unexplained electrocardiographic findings in patients revealing no evidence of coronary sclerosis and myocardial fibrosis. We believe that a study employing all the modern diagnostic methods may reveal a definite symptom complex and establish a clinical picture which has as its pathologic basis fatty infiltration of the myocardium.

#### SUMMARY

A short review of the literature on fatty infiltration of the myocardium is given, and a study of fifty-eight cases is reported. The myocardium of the right ventricle is the region mainly affected. The infiltration leads to a replacement of the muscle fibers by fatty tissue. The muscle fibers primarily become atrophic and later apparently disappear. If the replacement by fat involves a large portion of the myocardium it may lead to sudden death. Only if careful autopsy reveals the absence of all other major lesions may fatty infiltration of the myocardium be regarded as the sole cause of death. Two cases of this type are reported. There are two other cases in which replacement of the myocardium by fat was in all probability the cause of death. In one the diagnosis was pseudohypertrophic muscular dystrophy in which the fatty infiltration of the myocardium probably was a part of the general replacement of muscle with fat. In the second, the patient died after partial thyroidectomy. In twenty-nine instances, other pathologic changes, in addition to fatty infiltration of the myocardium, were found

at autopsy. In these cases, the lesion in the heart was thought to be a factor in hastening death. In twenty-five instances, fatty infiltration of the myocardium was an incidental finding at autopsy.

A clinical study of the patients reported on here reveals that fatty infiltration of the myocardium may cause death without any premonitory symptoms of heart failure. When such infiltration is present, factors which cause an increased demand on the heart and which under normal conditions could easily be compensated for may lead to sudden death. Fatty infiltration of the myocardium may be regarded as a morphologically demonstrable cause of heart failure and death in instances in which death clinically was thought to have been the result of functional disorders without a morphologic basis. Further study with exact clinical methods might establish a complex of signs and symptoms characteristic enough to warrant a clinical diagnosis of fatty infiltration of the myocardium.

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# CARDIAC WEIGHTS

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This study was undertaken to determine relative ventricular weights in cardiovascular syphilis. Interest in the wider problem of total cardiac weights and relative proportions of the various chambers in the important etiologic types of cardiac disease stimulated this more extensive investigation.

In any presentation of this subject, mention must be made of the classic work of Muller, whose monograph was published in 1883. His work was done on unfixed hearts, and, according to Lewis,<sup>1</sup> "the lines of the cuts are described in insufficient detail." We will not attempt a comparison of our figures with his. Lewis reported in 1913 a method of dividing and weighing the heart devised in a study of ventricular hypertrophy and preponderance. He deplored the tendency to diagnose relative hypertrophy from inspection alone and the fact that the method of weighing had not been adopted in teaching institutes and was not employed "by those who infer a large personal experience of hypertrophy in its relation to valvular or renal defects." He expressed the opinion that the usual clinical methods of demonstrating left and right ventricular preponderance "employed at the bedside are of little real value." His studies also supported the opinion that "it is probable that mechanical factors are by no means the only important causes of hypertrophy of the heart." In table 8, a comparison is made of our results with the summaries of the various groups published by Lewis.

The method employed in the weighing of the hearts here reported was devised and published by Herrmann.<sup>2</sup> Since his original article gives a complete description of his procedure, we shall merely summarize the essential features of the method.

The auricles and ventricles are separated by cutting along the auriculoventricular junction just above the valves (fig. 1). The circumflex branches of the coronary system are separated and pressed down on the ventricles. After removal of the auricles, the valves may be examined and tested by the water test. The auricular and ventricular portions of the heart are weighed separately, and the coronary

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1. Lewis, T.: *Heart* 5:367, 1913-1914.

2. Hermann, G. R.: *Am. Heart J.* 1:213, 1925.

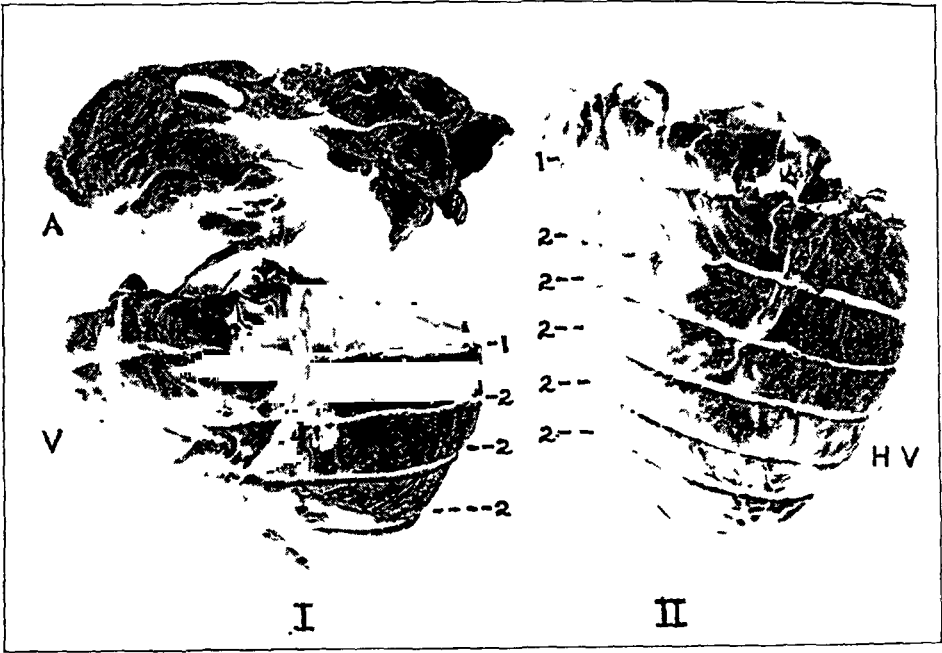


Fig. 1.—*I*, normal heart showing *A*, auricles; *V*, ventricles; *II*, hypertensive heart showing *HV*, hypertrophied ventricles; 1, incisions in the fat tissue for removing valves; 2, incisions in the myocardium for cutting ventricles into sections.

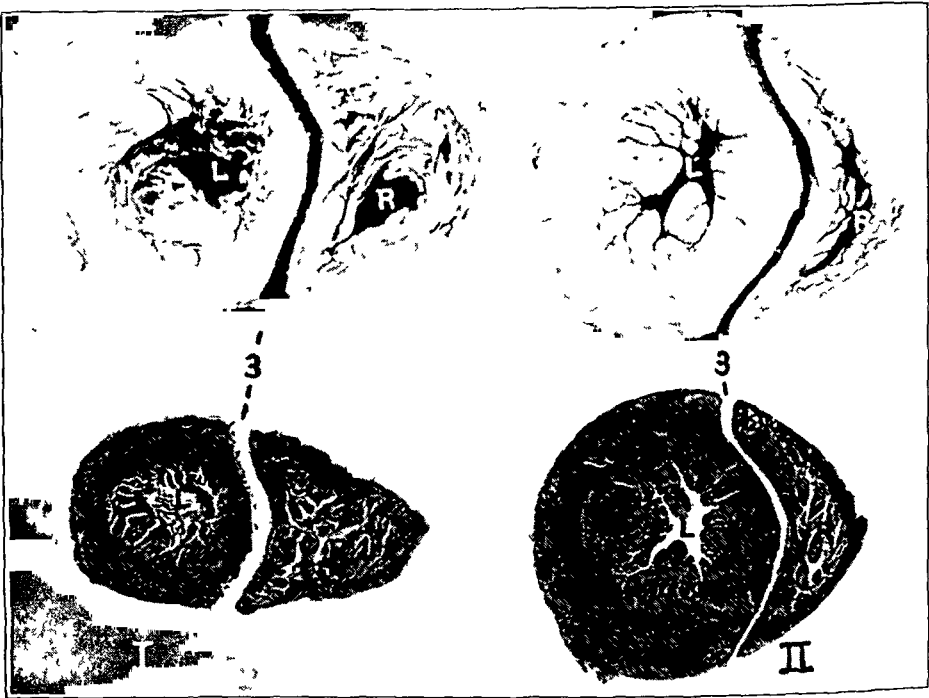


Fig. 2.—Corresponding sections from the two hearts in figure 1: *I*, normal heart; *II*, hypertensive heart; 3, incisions for separating the right and left portions of each section (divisions done before photographing); *L*, left ventricular portion; *R*, right ventricular portion.

TABLE 1.—Data Obtained on Normal Hearts <sup>1</sup>

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Case	Race	Sex	Age	BW	CA	FHW	FAW	FVW	XVW	LVW	RVW	LVW	FHW	FAW	FVW	XVW	LVW	RVW	
												Ra	BW	Ra	BW	Ra	BW	Ra	BW
1	W	M	45	41.7	72	234	31	203	165	95	70	1.357	0.00561	0.00074	0.00486	0.00395	0.00228	0.00168	
2	O	M	43	64.8	74	322	49	273	210	116	94	1.234	0.00497	0.00076	0.00420	0.00321	0.00179	0.00116	
3	O	F	35	46.1	64	229	37	192	133	90	43	2.095	0.00497	0.00080	0.00416	0.00288	0.00195	0.00093	
4	W	F	54	54.4	76	219	48	171	102	65	37	1.755	0.00403	0.00088	0.00314	0.00189	0.00119	0.00068	
5	W	F	42	59.3	61	218	31	187	121	77	44	1.750	0.00368	0.00052	0.00316	0.00204	0.00130	0.00071	
6	O	M	43	116.5	82	517	86	431	316	216	100	2.160	0.00414	0.00074	0.00370	0.00271	0.00185	0.00086	
7	O	M	36	61.6	70	285	45	240	200	125	75	1.667	0.00463	0.00073	0.00390	0.00324	0.00203	0.00122	
8	O	M	29	46.7	59	210	30	180	143	96	47	2.044	0.00450	0.00064	0.00385	0.00306	0.00206	0.00101	
9	O	M	42	49.8	80	280	40	249	184	121	63	1.920	0.00580	0.00080	0.00500	0.00369	0.00243	0.00126	
10	O	F	21	46.3	55	197	27	170	114	72	42	1.715	0.00425	0.00058	0.00367	0.00246	0.00155	0.00091	
Averages.....				39	58.7	69	272	42	230	169	62	1.770	0.00469	0.00072	0.00396	0.00292	0.00184	0.00108	

\* In this and the following tables BW indicates body weight in kilograms; CA, supra-ventricular aortic circumference in millimeters; FHW, fresh heart weight in grams; FAW, fresh auricular weight in grams; FVW, fresh ventricular weight in grams; XVW, ventricular weight in grams after cleaning and fixation; LVW, left ventricular weight in grams after cleaning and fixation; RVW, right ventricular weight in grams after cleaning and fixation; Ra, ratio (both factors in all ratios being in grams).

The blood pressure values will be found in column 3a in tables 3, 4 and 5.

arteries are opened and examined. The ventricles are fixed in a dilute solution of formaldehyde, U. S. P. (1:10), after which these are weighed at intervals until the weight (which at first rises slightly in the process of fixing) returns to the original value. The valves are then removed as a single plate. In figure 1, this cut is shown by incision 1. After the incision is made, the epicardium, fat and vessels are reflected back to the valve rings, and the latter are cut away from the muscle, the chordae tendineae being cut at the tips of the papillary muscles. The remaining epicardium, fat and vessels are then removed from the ventricles, leaving only the musculature.

The ventricles are next divided into sections by a series of parallel cuts (fig. 1, incision 2) at right angles to the long axis. In figure 1, to the left, is shown a normal heart which required only three cuts, while a hypertensive heart, to the right, required five. Each ventricular section is then separated by division at the septum into right and left components (fig. 2, incision 3). The attempt is made to make the septal division proportional to the width of the lateral walls of the ventricles. This closely approximates the midseptal line as the term is used by Herrmann. For accuracy of division, it is advisable to have the sections thin, especially in markedly hypertrophied hearts where the septum is apt to bulge into the right ventricle. The segments of ventricle thus derived are weighed. In figure 2 are pictured corresponding segments of the hearts shown in figure 1. The illustration demonstrates the hypertrophy.

#### NORMAL HEARTS

For purposes of comparison, ten hearts acceptable as normal were included in the study. Table 1 shows the data obtained from these. In three instances death occurred from acute pneumonia; in five, from acute generalized peritonitis; in one, from a ruptured gastric ulcer, and in the last, from suppurative leptomeningitis.

On the basis of our results, the average total weight of the heart for a person of 58.7 Kg. (127 pounds) is 272 Gm. The average auricular weight for the same group is 42 Gm.; the left ventricular weight after cleaning and fixation, 107 Gm., and the right ventricular weight after cleaning and fixation, 62 Gm. The L/R ratio (left to right ventricle) is 1.770. The ratio of total cardiac weight to body weight is 0.00469; of auricular weight to body weight, 0.00072, and of ventricular weight, after cleaning and fixation, to body weight, 0.00184 for the left ventricle and 0.00108 for the right.

Table 1 *A* presents a comparison of our figures with those of Herrmann, showing similar data from dogs' hearts. It appears that the L/R ratio is greater in man (column 12), while in other respects the figures are uniformly higher for the hearts of dogs. Maximum and minimum figures for the hearts included in the various groups are presented.

#### WASTING DISEASES

Table 2 includes the figures on the hearts of ten patients who died of other than cardiac diseases. Their conditions may be correctly designated as "wasting diseases." Of these patients, four died of carci-

noma and six of tuberculosis. Of the latter, two died of tuberculous meningitis, two of ulcerative pulmonary tuberculosis, one of tuberculous peritonitis and one of tuberculous bronchopneumonia. In all, the subepicardial fatty tissue showed serous atrophy. The average body weight is only 43.3 Kg. and the heart weight, 210 Gm. The L/R ratio and the weights of the cardiac chambers proportional to the body weight are slightly higher than in the normal group. Apparently, in wasting diseases of some duration associated with progressive and marked loss of body weight, the weight of the heart is relatively well maintained.

#### HYPERTENSIVE HEARTS

Table 3 presents the data on ten hypertensive hearts. A column including the blood pressure readings recorded on the clinical charts has been added. None of these patients had valvular lesions. On the

TABLE 1 A.—*Comparison of Normal Human and Normal Dog Hearts\**

	12	13	14	15	16	17	18
	LVW	FHW	FAW	FWW	XVW	LVW	RVW
	Ra—	Ra—	Ra—	Ra—	Ra—	Ra—	Ra—
	RVW	BW	BW	BW	BW	BW	BW
Averages							
Human hearts.....	1.770	0.00469	0.00072	0.00396	0.00292	0.00184	0.00108
Dog hearts (Herrmann)	1.398	0.00798	0.00097	0.00789	0.00635	0.00369	0.00265
Maximum							
Human hearts.....	2.160	0.00580	0.00088	0.00500	0.00395	0.00243	0.00168
Dog hearts (Herrmann)	1.773	0.00994	0.00156	0.00905	0.00872	0.00472	0.00400
Minimum							
Human hearts.....	1.234	0.00368	0.00052	0.00314	0.00189	0.00119	0.00068
Dog hearts (Herrmann)	1.153	0.00600	0.00056	0.00512	0.00467	0.00268	0.00178

\* Average of heart weights of fifteen normal dogs.

basis of the pathologic changes, in four instances death was due to malignant nephrosclerosis, once to primary contracted kidney, once to acute glomerulonephritis engrafted on a benign arteriosclerosis, three times to red encephalomalacia associated with hypertension and once to severe essential hypertension. In no case was congestive cardiac failure present. In this group the blood pressure varied from 176 systolic and 90 diastolic to 260 systolic and 170 diastolic. The average body weight in this group was 59 Kg., practically the same as that found in the normal group. The cardiac weights are well above normal. The average cardiac weight is 472 Gm. The ventricular weight (average) after cleaning and fixation is 328 Gm. With essentially the same body weights, the average total heart weight in the hypertensive group is 1.73 times the same weight in the normal group, and the average ventricular weight after cleaning and fixation is 1.94 times the same weight in the normal group. Furthermore, comparison of the ventricular weights after cleaning and fixation shows that the average weight of the left ventricle in the hypertensive group is 2.21 times the

TABLE 2.—Data on Hearts in Wasting Diseases

Case	Race	Sex	Age	BW	CA	FHW	FAW	FWW	JXVW	LVW	RVW	Ra	LWV	FHW	Ra	FAW	Ra	FWW	Ra	XVW	Ra	LVW	Ra	RVW	Ra
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
11	O	M	43	58.4	72	257	37	220	167	103	64	0.00440	0.00063	0.00377	0.00286	0.00176	0.00110								
12	W	M	59	54.4	85	243	36	207	150	94	56	0.00447	0.00066	0.00380	0.00276	0.00173	0.00103								
13	W	M	53	38.1	80	172	30	142	95	65	30	0.00451	0.00079	0.00373	0.00249	0.00171	0.00079								
14	O	M	25	43.1	56	198	27	171	132	93	39	0.00459	0.00063	0.00397	0.00306	0.00216	0.00090								
15	Mex	M	29	34.0	52	179	20	159	125	82	43	0.00525	0.00039	0.00465	0.00368	0.00241	0.00126								
16	W	M	62	45.8	91	223	43	180	139	90	49	0.00487	0.00094	0.00392	0.00363	0.00196	0.00107								
17	O	M	56	36.3	82	204	31	173	132	82	50	0.00562	0.00085	0.00476	0.00364	0.00226	0.00138								
18	W	M	53	49.8	67	267	40	227	155	98	57	0.00536	0.00080	0.00456	0.00311	0.00197	0.00114								
19	W	M	61	42.2	73	217	38	179	152	85	67	0.00514	0.00090	0.00424	0.00360	0.00262	0.00159								
20	O	F	54	30.4	71	140	21	119	85	53	32	0.00460	0.00069	0.00391	0.00280	0.00174	0.00105								
Averages.....				43.3	73	210	32	178	133	85	49	0.00488	0.00075	0.00413	0.00310	0.00197	0.00113								

TABLE 3.—Data on Hypertensive Hearts

Case	Race	Sex	Age	Blood Pressure	BW	CA	FHW	FAW	FWW	XVW	LVW	RVW	Ra	LWV	FHW	FAW	FWW	XVW	LVW	RVW	Ra	BW	RVW
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
21	C	F	45	180/124	49.0	61	445	78	367	271	181	90	2.010	0.00908	0.00159	0.00750	0.00553	0.00369	0.00184				
22	W	F	30	250/140	64.3	69	501	59	442	366	279	87	3.210	0.00778	0.00092	0.00687	0.00569	0.00434	0.00135				
23	W	F	34	176/90	50.8	60	330	48	282	218	153	65	2.353	0.00650	0.00094	0.00355	0.00429	0.00301	0.00128				
24	W	F	45	260/138	47.2	67	421	61	360	265	190	75	2.530	0.00891	0.00128	0.00762	0.00562	0.00402	0.00159				
25	C	F	43	260/170	65.2	78	467	60	407	339	269	70	3.840	0.00717	0.00092	0.00623	0.00520	0.00412	0.00107				
26	C	M	56	.....	79.3	90	513	78	435	356	260	96	2.707	0.00647	0.00098	0.00548	0.00448	0.00328	0.00121				
27	W	M	66	210/110	65.7	92	533	78	455	333	217	116	1.872	0.00812	0.00119	0.00693	0.00507	0.00330	0.00177				
28	C	M	50	250/156	65.2	75	667	77	590	527	360	167	2.155	0.01022	0.00118	0.00905	0.00807	0.00552	0.00256				
29	C	M	27	236/170	39.9	60	300	28	272	236	183	53	3.450	0.00752	0.00070	0.00681	0.00591	0.00458	0.00133				
30	C	G	29	225/125	63.4	69	538	70	468	368	274	94	2.015	0.00849	0.00110	0.00748	0.00581	0.00432	0.00148				
Averages.....				.....	59.0	72	472	64	403	328	237	91	2.704	0.00803	0.00108	0.00695	0.00537	0.00402	0.00155				

same weight in the normal group, and that the average right ventricular weight in the hypertensive group is 1.48 times the weight of the same chamber in the normal group. These figures clearly indicate that the ventricular hypertrophy of hypertensive heart disease mainly involves the left ventricle. The L/R ratio in this group is 2.704; the ratio of the fresh heart weight to the body weight is notably greater than in the normal group.

#### RHEUMATIC HEARTS

Table 4 includes the figures obtained on examination of fifteen hearts in which rheumatic heart disease was present. The first subgroup consists of five hearts with mitral stenosis and regurgitation. The blood pressure ranges from 80 systolic and 60 diastolic to 136 systolic and 78 diastolic. The average fresh heart weight is 476 Gm., more than the average fresh heart weight in the hypertensive group, and 1.75 times the weight of the average heart in the normal group. Because of the greater average body weight in this group, the heart weight-body weight ratio is less than in the hypertensive group. In this connection, mention should be made of the probable influence of general anasarca, so common in rheumatic heart disease, in increasing the body weight and thus altering the significance of our figures. It is noteworthy that in this group the average auricular weight is 2.71 times the normal average, and the right ventricular weight is 2.21 times the normal, while the left ventricular weight is only 1.32 times that of the average left ventricular weight in the normal group. The L/R ratio here is only 1.070, as against the normal of 1.770. In two instances the right ventricle weighed more than the left; in these two cases (32 and 33) and in case 31, the most marked valvular deformities were found. In this group the ratios of the fractional heart weights to the body weight are all well above the normal.

In this small group the ratios of the various weights to the body weights show wide variations. The maximum and minimum figures are those for cases 35 and 32; in the former, the body weight was only 39.4 Kg.; in the latter, 128.2 Kg. The hearts were about of equal gross weight in the fresh state. In both instances, however, the evidence of disproportionate auricular and right ventricular weight is demonstrable. In case 32, the absolute fresh auricular weight is 2.14 times that of the average in the normal group, and the right ventricular weight is 2.74 times that of the normal average; the ratio of right ventricular weight to body weight is 0.00132 as compared with the normal of 0.00108, while the total heart weight (fresh) is 1.76 times the normal average, and the left ventricular weight is 1.13 times the normal average. The ratio of left ventricular weight to body weight is 0.00094 as compared with the normal of 0.00184. In case 35, the absolute fresh auricular weight is 3.16 times the normal average, the



TABLE 4.—Data on Rheumatic Hearts

1	2	3	3a	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Case	Rate	Sex	Age	BW	CA	PHW	FAW	FWW	XVW	LVW	RVW	Ra	FWW	FAW	FWW	XVW	LVW	RVW
			Blood Pressure															
Mitral Stenosis and Regurgitation																		
31	W	M	58	78.8	77	393	96	297	227	132	95	1.359	0.00497	0.00122	0.00377	0.00288	0.00167	0.00121
32	O	F	42	128.2	73	482	90	392	291	121	170	0.712	0.00376	0.00070	0.00305	0.00226	0.00094	0.00132
33	W	M	40	84.7	70	540	158	382	278	190	158	0.759	0.00637	0.00186	0.00451	0.00328	0.00142	0.00186
34	O	M	41	67.0	62	518	88	480	340	193	147	1.312	0.00774	0.00131	0.00642	0.00507	0.00288	0.00219
35	O	F	19	39.4	61	456	133	323	254	138	116	1.179	0.01188	0.00338	0.00820	0.00644	0.00350	0.00294
Averages.....				40	69	476	113	365	278	141	137	1.070	0.00638	0.00169	0.00519	0.00398	0.00208	0.00190
Aortic Stenosis and Regurgitation																		
36	O	M	40	71.6	75	635	82	553	438	259	149	1.940	0.00887	0.00115	0.00772	0.00612	0.00404	0.00208
37	W	M	55	80.7	92	604	90	514	406	289	147	1.762	0.00748	0.00111	0.00636	0.00503	0.00321	0.00182
38	W	M	56	35.4	63	334	34	300	265	138	107	1.477	0.00944	0.00096	0.00846	0.00749	0.00446	0.00302
Averages.....				50	77	524	69	456	369	235	134	1.726	0.00859	0.00107	0.00751	0.00621	0.00390	0.00231
Mitral and Aortic Stenosis and Regurgitation																		
39	W	M	32	52.1	66	846	106	740	568	440	128	3.440	0.01624	0.00204	0.01421	0.01090	0.00845	0.00246
40	W	M	64	52.5	105	605	88	517	412	266	146	1.882	0.01151	0.00168	0.00985	0.00785	0.00507	0.00278
41	W	M	21	57.5	53	463	61	402	327	225	102	2.205	0.00805	0.00106	0.00700	0.00569	0.00392	0.00177
42	W	M	40	144.9	81	601	90	511	431	291	140	2.080	0.00840	0.00126	0.00714	0.00603	0.00407	0.00196
43	W	F	45	76.5	60	434	97	337	243	137	106	1.292	0.00587	0.00128	0.00441	0.00318	0.00179	0.00139
Averages.....				40	73	590	88	501	396	272	124	2.168	0.00997	0.00146	0.00852	0.00673	0.00466	0.00207
Mitral, Aortic and Tricuspid Stenosis and Regurgitation																		
44	O	M	57	58.9	66	396	90	306	220	143	77	1.855	0.00672	0.00153	0.00519	0.00374	0.00242	0.00131
Thrombo-Endocarditis of Mitral Valve, No Old Valvular Deformity																		
45	O	F	39	40.8	60	236	36	200	145	95	50	1.900	0.00578	0.00098	0.00469	0.00355	0.00233	0.00122

right ventricular weight is 1.87 times the normal average, and the ratio of right ventricular weight to body weight is 0.00294 as compared with the normal 0.00108, while the fresh total heart weight is only 1.67 times the normal, and the left ventricular weight is 1.29 times the average normal. The ratio of left ventricular weight to body weight is 0.00350 as compared with the normal of 0.00184.

In this connection, attention may be called to an item of importance in the determination of right ventricular hypertrophy. Normally, the right ventricle is from 2 to 4 mm. thick. With an increase of thickness of only 2 mm., the right ventricle becomes twice the normal weight because of its large surface area. With an increase of weight of the left ventricle sufficient to double the normal, the thickness of the ventricular wall may be as much as 18 mm. instead of from 12 to 14 mm. Because this slight increase of thickness of the right ventricle is often disregarded, actual hypertrophy of the wall is apt to be overlooked (personal communication from Dr. R. H. Jaffé).

In the second group are presented the figures on three hearts with rheumatic disease confined to the aortic valve. The average weight of these hearts is 524 Gm., which is 1.93 times the average heart weight in the normal group, while the left ventricle in this group averages 2.18 times the weight of the average normal left ventricle, and the right is 2.16 times the normal average. The average auricular weight is 1.64 times the average of the normal group. The L/R ratio is 1.726. The group is so small that conclusions must be stated with caution. The findings confirm doubts which have been expressed from time to time as to the necessary connection of hypertrophy with mechanical strain. The simultaneous increase of the auricles and right ventricles as revealed in the average results points to other causes of the increase in size.

Five hearts with both mitral and aortic rheumatic lesions are included in the third subgroup of table 4. In only one instance was the blood pressure over 148; in this case it was 172. Though the average body weight of this group is close to that of the normal average, the fresh heart weight is more than twice that of the normal. There is a wide variation in the individual heart weights of this group. The wide gross variations are accompanied by similar figures for the L/R ratios. The average values, as may be seen, are decidedly high. Attention may also be drawn to the considerable increase in the figures for the ratios of the various cardiac segments to the body weights.

There remain two hearts of the rheumatic group. The first (case 44) is the only one which had a marked fibroplastic deformity of the mitral, aortic and tricuspid valves. This heart weighed 396 Gm. The segmental figures show essentially uniform increase of the various chambers. The body weight was normal.

The second of these two hearts was removed from the body of a woman of 39, dead of pneumonia and meningitis. The absolute and relative weights of this heart do not vary widely from the normal. This heart was put aside as a normal heart until opened; then a recent thrombo-carditis of the mitral valve was discovered. There was no evidence of an old endocarditis. The findings in this heart are of interest in connection with those in four others (cases 34, 36, 37 and 41) in all of which the valves involved in the chronic process showed the presence of recent thrombo-endocarditis. The heart in case 45 is presented as evidence that recent acute infections are not responsible for hypertrophy; the hypertrophy of the four hearts just mentioned (included in the tables of hearts with chronic disease) developed as a result of chronic disease, irrespective of the terminal fresh infection. With the exception of case 45, all of the hearts in the rheumatic group were removed from the bodies of persons who had presented cardiac decompensation. In case 33, a ruptured duodenal ulcer with infected ascites was found at autopsy which had been overlooked clinically in the presence of congestive failure.

#### SYPHILITIC HEARTS

The first subgroup includes the hearts in which anatomic aortic insufficiency was demonstrated. The second subgroup presents the figures for our hearts showing syphilitic aortitis with cardiac hypertrophy, and the third presents the results for four hearts with syphilitic aortitis without regurgitation or hypertrophy. The fifteen hearts in subgroups 1 and 2 were all from patients who had had cardiac failure of the congestive type. One died of red encephalomalacia and one from gastric ulceration with hemorrhage. In case 57, the cardiac disease was complicated by miliary tuberculosis. The diagnosis of syphilitic aortitis was accepted only when the gross appearances were confirmed by microscopic findings.

In the eleven hearts in the first subgroup aortic insufficiency was demonstrated by the water test. Definite valvular deformities were present. The blood pressure readings ranged from 214 systolic and 60 diastolic to 115 systolic and 85 diastolic. In two instances the pulse pressure was lower than the expected normal; in the other nine, the pulse pressure was high, although in cases 53 and 56 it was not notably so. In this group, in every instance the heart was markedly hypertrophied. The smallest heart in the group weighed 450 Gm., and the ratio of fresh heart weight to body weight in this case was 0.00903 as compared with the normal of 0.00470. The average fresh heart weight was 661 Gm., and the average ratio of fresh heart weight to body weight was 0.00992, more than twice the normal. The average L/R

ratio is 2.190 as compared with the normal average of 1.770; in this group of hearts with aortic insufficiency there is obviously a disproportionate increase of left ventricular weight. The ratios of the total and fractional weights are all above the normal. The average auricular weight as compared with the body weight is 0.00130, while the normal ratio is 0.00072; the ratio of left ventricular weight to body weight is 0.00504 as compared with the normal of 0.00184, and the ratio of right ventricular weight to body weight is 0.00227, while the normal average is 0.00108.

The various weights and ratios seen in subgroup 2 are strikingly similar to those of the first subgroup. The average heart weight is slightly less in the second group. The L/R ratio is about the same in each group. The ratios of fresh heart weight to body weight, of fresh auricular weight to body weight and of fresh ventricular weight to body weight are remarkably close. This is also true of the ratio of right ventricular weight to body weight, but the ratios of ventricular weight after cleaning and fixation and of left ventricular weight to body weight are not so much alike: In each instance these are less in the group without aortic regurgitation. Perhaps it should be noted that the patient in case 62 died after four months in the hospital, during all of which time his heart was decompensated. His death, however, followed a gastric hemorrhage, and subacute peptic ulcers of the stomach were found at autopsy. In this group of four, the blood pressure was distinctly high in two and moderately increased in a third.

The cardiac hypertrophy of this group may be ascribed to hypertension in three of the four cases: The patient in case 64 not only had a systolic pressure of 200, but died of red encephalomalacia, and at autopsy was found to have benign arteriosclerosis and arteriolosclerosis. The fourth case is worthy of some discussion. In spite of low blood pressure, the heart was very large. The senior intern had noted a diastolic murmur at the aortic area: the hospital chart contained no confirmatory note by the attending physician. The circumference of the aorta was notably large. This case suggests the possibility of relative aortic regurgitation during life, a subject which is occasionally raised between the clinician and the pathologist.

In the third subgroup are included four hearts from the bodies of persons with syphilitic aortitis without deformity of the aortic valves, aortic regurgitation (anatomic) or cardiac hypertrophy. In one instance there was a definite aneurysm of the arch. The figures recorded in table 5 are strikingly similar to those for the normal group, except for those of the left ventricle and the aorta. The circumference of the aorta is wider in the syphilitic group than in the normal. The L/R ratio is 2.099 (within the normal range) for this group, as compared with 1.770 for the average normal.

TABLE 5.—Data on Syphilitic Hearts

1	2	3	3a	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Case	Race	Sex	Age	BW	CA	FHW	FAW	FVW	XVW	LVW	RVW	Ra	Lvw	FHW	FAW	Ra	XVW	RVW
			Blood Pressure															
Syphilitic Aortitis with Aortic Regurgitation																		
51	W	M	46	83.8	85	1,004	129	875	677	469	208	2,250	0.01190	0.00154	0.01040	0.00309	0.00559	0.00248
52	C	M	44	74.8	90	644	86	558	472	318	154	2,065	0.00861	0.00115	0.00746	0.00632	0.00425	0.00206
53	C	M	52	92.9	88	776	102	688	478	478	210	2,275	0.00945	0.00110	0.00835	0.00741	0.00515	0.00226
54	C	M	57	43.0	87	460	329	402	329	228	101	2,260	0.01070	0.00135	0.00935	0.00765	0.00530	0.00235
55	C	M	53	50.7	95	783	81	702	627	471	156	3,020	0.01540	0.00159	0.01383	0.01237	0.00929	0.00308
56	C	M	58	66.2	115	635	90	545	456	322	134	2,402	0.00958	0.00136	0.00823	0.00888	0.00502	0.00202
57	C	M	63	165/90	82	557	82	475	391	288	183	1,940	0.00351	0.00083	0.00495	0.00407	0.00269	0.00139
58	C	M	53	98.0	104	557	80	550	475	322	153	2,105	0.01110	0.00141	0.00971	0.00887	0.00568	0.00270
59	C	M	29	56.7	65	530	50	540	474	299	175	1,710	0.00845	0.00131	0.00714	0.00627	0.00396	0.00232
59	C	M	42	75.6	140	639	63	540	474	299	175	1,710	0.00845	0.00131	0.00714	0.00627	0.00396	0.00232
60	W	M	42	49.8	87	450	69	387	308	211	97	2,175	0.00903	0.00127	0.00777	0.00618	0.00424	0.00197
61	C	M	73	65.3	90	591	88	503	445	291	154	1,890	0.00906	0.00135	0.00770	0.00681	0.00446	0.00236
Averages.....			136/52	68.6	95	661	87	574	486	333	152	2,190	0.00892	0.00130	0.00863	0.00751	0.00504	0.00227
Syphilitic Aortitis Without Aortic Regurgitation, but With Hypertrophy of Heart																		
62	C	M	57	52.6	113	709	100	609	513	316	197	1,605	0.01348	0.00192	0.01159	0.00974	0.00601	0.00374
63	C	M	56	64.3	105	617	73	541	452	333	119	2,739	0.00639	0.00113	0.00545	0.00702	0.00517	0.00185
64	W	M	77	200/80	64	468	88	378	231	189	72	2,205	0.00708	0.00134	0.00352	0.00242	0.00219	0.00110
65	C	M	42	61.2	170	610	99	511	416	282	134	2,102	0.00997	0.00162	0.00835	0.00679	0.00460	0.00219
Averages.....			126/60	60.9	125	601	90	511	403	273	131	2,178	0.01003	0.00125	0.00853	0.00677	0.00455	0.00222
Syphilitic Aortitis Without Aortic Regurgitation and Without Hypertrophy of Heart																		
66	C	M	44	64.8	70	345	47	295	229	160	69	2,320	0.00532	0.00072	0.00460	0.00354	0.00247	0.00106
67	C	M	55	130/80	130	280	46	234	196	137	59	2,820	0.00342	0.00089	0.00453	0.00380	0.00265	0.00114
68	W	M	67	112/60	80	272	36	236	177	120	57	2,105	0.00387	0.00051	0.00352	0.00252	0.00171	0.00081
69	W	M	42	136/68	75	298	39	259	199	124	75	1,652	0.00487	0.00064	0.00423	0.00325	0.00202	0.00123
Averages.....			52	61.9	89	299	42	257	200	135	65	2,099	0.00487	0.00069	0.00418	0.00328	0.00221	0.00106

## COMMENT

Table 6 presents a summary of the averages presented in the preceding tables. Former subgroups are given under numbers applicable to this table alone. The greatest average body weight is found in group 4 (rheumatic hearts with mitral disease). The probability of the influence of general edema has been referred to. The aortic circumferences are larger in the syphilitic groups. The heaviest hearts were found in group 7 followed by groups 8 and 6. Group 5 is the only other group in which the average heart weight was over 500 Gm. The average weight of the hearts in the hypertensive group is almost exactly equal to that of the rheumatic hearts with mitral valvular disease. The tables justify the conclusion that aortic regurgitation is the lesion most important in the production of extreme cardiac hypertrophy, and left ventricular enlargement is disproportionately great in these cases.

The highest average auricular weight is found in group 4 (113 Gm.). The highest ventricular weights are found in group 7, in which both left and right ventricular weights exceed those of any other group. The left ventricular weight is disproportionate, as shown by the high L/R ratio. Interesting are the figures for group 4 (rheumatic hearts with mitral deformity) in which the left ventricle is enlarged, actually and proportionately to the body weight, yet the right ventricle is almost as heavy as the left. The L/R ratio is the lowest recorded, 1.070. In group 2 (wasting diseases), the actual weights are less than the normal, but the total and fractional weights in relation to the body weight are above the normal average.

While the absolute cardiac weights of the hypertensive group (group 3) are not those of maximum increase, nevertheless the figures are interesting. The L/R ratio is the largest determined, 2.704 as compared with the normal 1.770. The actual left ventricular weight is 2.21 times the normal, while the right ventricular weights average only 1.48 times those of the normal group. The ratio of left ventricular weight to body weight is, in group 3, 2.18 times that in group 1, and that of right ventricular weight to body weight is 1.43 times that of group 1. Most of the hearts in group 3 were from patients who had died of renal disease. Our figures are not in agreement with the statement of Lewis that renal disease is associated with uniform enlargement of the ventricles. Our results are strictly in agreement with another statement of Lewis to the effect that a rise of blood pressure is important in the production of preponderance of the left ventricle, since the highest blood pressures are recorded in this group. The L/R ratios are high and about equal in groups 6, 7 and 8. The second and fifth groups show an L/R ratio about normal; this ratio in the latter group

TABLE 6.—*Summary of Averages*

1	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Age	BW	OA	FHW	FAW	FVW	XVW	LVW	RVW	Ra	RVW	Ra	BW	Ra	BW	Ra
Group 1. Normal .....	39	58.7	69	272	42	230	169	107	1.770	0.00469	0.00072	0.00306	0.00292	0.00184	0.00103
Group 2. Wasting diseases .....	50	43.3	73	210	32	178	133	85	1.788	0.00488	0.00075	0.00413	0.00310	0.00197	0.00113
Group 3. Hypertensive hearts.....	43	59.0	72	472	64	408	328	237	2.704	0.00803	0.00108	0.00695	0.00557	0.00402	0.00155
Group 4. Rheumatic hearts: deformity of mitral valve.....	40	79.6	69	476	113	365	278	141	1.070	0.00688	0.00169	0.00519	0.00308	0.00208	0.00190
Group 5. Rheumatic hearts: deformity of aortic valve.....	50	62.6	77	524	69	456	369	235	1.726	0.00859	0.00107	0.00751	0.00621	0.00390	0.00231
Group 6. Rheumatic hearts; deformities of mitral and aortic valves...	40	62.0	73	590	88	501	396	272	2.168	0.00997	0.00146	0.00852	0.00673	0.00466	0.00207
Group 7. Syphilitic hearts with aortic regurgitation .....	51	68.6	95	661	87	574	486	333	2.190	0.00992	0.00130	0.00863	0.00731	0.00504	0.00227
Group 8. Syphilitic hearts without aortic regurgitation, but with hyper- trophy .....	57	60.9	125	601	90	511	403	273	2.178	0.01003	0.00125	0.00853	0.00677	0.00455	0.00222
Group 9. Syphilitic hearts without aortic regurgitation or hypertrophy	52	61.0	89	299	42	257	200	135	2.099	0.00487	0.00069	0.00418	0.00328	0.00221	0.00106

may be interpreted as indicating uniform hypertrophy of the ventricles in cases of rheumatic disease with aortic involvement.

Table 7 presents a recapitulation of the increase in the average values of total and fractional weights relative to body weights as shown in all the abnormal groups in comparison with the normal. In group 2, the increase over normal values ranges from 1.04 to 1.07, a moderate increase which is obviously due to the relative decrease of body weight in wasting diseases. In group 4, the inference is clear that the cardiac enlargement is mainly due to the marked increase in weight of the auricles and the right ventricle as contrasted with an increase of the left ventricular weight of minor degree. The contrary is shown by the exaggerated hypertrophy of the left ventricle in the hypertensive group.

TABLE 7.—Increase of Average Ratios Over Normal Values

	12 LVW Ra— RVW	13 FHW Ra— BW	14 FAW Ra— BW	15 FVW Ra— BW	16 XVW Ra— BW	17 LVW Ra— BW	18 RVW Ra— BW
2. Wasting diseases .....	1.01	1.04	1.04	1.04	1.05	1.07	1.05
3. Hypertensive hearts .....	1.53	1.71	1.50	1.75	1.91	2.18	1.43
4. Rheumatic hearts: deformity of mitral valve....	0.60	1.47	2.34	1.31	1.36	1.13	1.76
5. Rheumatic hearts: deformity of aortic valve....	0.98	1.83	1.49	1.90	2.13	2.12	2.14
6. Rheumatic hearts; deformities of mitral and aortic valves .....	1.23	2.12	2.03	2.15	2.30	2.53	1.92
7. Syphilitic hearts with aortic regurgitation ...	1.24	2.11	1.80	2.18	2.50	2.74	2.10
8. Syphilitic hearts without aortic regurgitation, but with hypertrophy..	1.23	2.14	1.74	2.15	2.32	2.48	2.06
9. Syphilitic hearts without aortic regurgitation or hypertrophy .....	1.19	1.04	0.94	1.06	1.12	1.20	0.97

In the last four groups of table 7, the left ventricle was enlarged. In group 5, the proportionate increase in weight of the two ventricles was about the same, although the valvular deformity was confined to the aortic valves with both regurgitation and stenosis; the increase of ventricular weight was much greater than that of the auricles. In groups 6, 7 and 8, the first group with rheumatic disease and aortic as well as mitral involvement, and the other two groups with syphilitic disease, one with aortic regurgitation and the other with hypertension, the proportionate increase in the weight of the left ventricle was greater than that of the right. In group 6, increase of the auricular (combined) weight was greater than that of the right ventricle, but less than that of the left. In groups 7 and 8, the increase of auricular weight was distinctly less than that of ventricular weight. The last three groups show an almost identical proportionate increase of the ratio of fresh heart weight to body weight, 2.12, 2.11 and 2.14. While the number of



TABLE 8.—*Comparison of Authors' Values and Lewis' Values for Human Hearts*

Group	Type of Heart	Name of Investigator	Name of Group	Number of Hearts	Body Weight, Kg.	Heart Weight, Gm.					L/R Ratio			Number With Value Below One
						Total	Ventricles			Septal	Average	Maxi- mum	Mini- mum	
							Both	Left	Right					
1	Normal	Authors Lewis	Normal Control	10 12	58.7 40.6	272 285	169.0 156.1	107.0 82.4	62.0 46.7	.... 27.0	1.770 1.790	2.160 2.180	1.234 1.570	.. ..
2	No hypertrophy	Authors Lewis	Wasting diseases Cancer	10 11	43.3 49.4	210 304	133.0 148.7	85.0 81.4	49.0 44.2	.... 23.1	1.788 1.830	2.382 2.060	1.270 1.470	.. ..
3	No valvular lesions	Authors Lewis Lewis Lewis	Hypertension Contracted kidney Interstitial nephritis Renal involvement	10 10 8 9	59.0 67.0 53.0 74.1	472 516 612 550	328.0 285.5 352.3 314.4	237.0 154.5 204.7 170.8	91.0 84.2 94.6 94.7	.... 46.5 53.0 48.9	2.704 1.870 2.170 1.910	3.840 2.440 2.410 2.470	1.872 1.080 1.840 1.070	.. .. .. ..
4	Mitral lesions	Authors Lewis	Mitral stenosis and regurgitation. Mitral stenosis	5 16	79.6 55.7	476 488	278.0 256.7	141.0 117.0	137.0 97.3	.... 42.5	1.070 1.550	1.389 2.850	0.712 0.320	2 5
5	Mitral and aortic lesions	Authors Lewis Lewis	Mitral and aortic stenosis and re- gurgitation Mitral stenosis with slight aortic lesions Mitral stenosis and aortic disease	5 6 11	62.0 .... 58.7	590 492 520	396.0 242.8 305.1	272.0 137.0 162.3	124.0 69.2 94.0	.... 36.6 48.8	2.168 2.230 1.710	3.440 3.430 2.560	1.292 0.520 1.130	.. 1 ..
6	Aortic lesions	Authors Authors Lewis	Syphilitic with aortic regurgita- tion Rheumatic aortic stenosis and re- gurgitation Aortic disease	11 3 13	68.6 62.6 66.0	661 524 713	486.0 369.0 421.7	333.0 235.0 241.7	152.0 134.0 112.7	.... .... 67.3	2.190 1.726 2.150	3.020 1.940 3.440	1.710 1.477 1.270	.. .. ..

hearts examined is small, it appears that the hypertrophy in both types of syphilitic hearts is such that the entire organ undergoes hypertrophy, although the increase in size of the left ventricle is disproportionate. One may conclude that the mechanical factors of regurgitation are not the only ones involved in the production of cardiac enlargement. The similarity of the figures in groups 7 and 8 also signifies that valvular insufficiency is not the only cause of cardiac enlargement in syphilitic hearts. That hypertension is not the only other factor is indicated by the figures for the two hearts from persons who had, during life, pressures within normal limits.

Table 8 shows a comparison of values obtained by Lewis and by us. The column for septal weights is included because Lewis weighed the septum separately. In calculating the L/R ratio, he did not take the septal weight into consideration. Generally speaking, these figures are not widely at variance. The small number of hearts in some of the groups may account, partly, for the difference in results. Herrmann estimated the L/R ratio for the hearts of dogs by his own method and by that of Lewis, and found that the method of Lewis gave slightly higher figures, 1.398 for Herrmann's method compared with 1.461 for that of Lewis. Lewis makes the statement that hypertrophy of the left ventricle alone is rare in aortic disease; in such hearts uniform hypertrophy is as frequent as hypertrophy with preponderance of the left ventricle. These statements are supported by our findings. In all cases of aortic valvular involvement included here, the heart showed hypertrophy of both ventricles. In sixteen hearts with rheumatic or syphilitic involvement of the aortic valves, the L/R ratio is within the normal range in eleven; the other five show an L/R distinctly above what may be regarded as normal.

The greatest discrepancy in the two sets of figures appears in the hypertensive and nephritic groups without valvular lesions. Eight of the ten hearts of our hypertensive group were found in association with definite renal change. Of these eight, the L/R ratios of only two were found within the normal range. Lewis found in practically all nephritic persons a normal L/R ratio and uniform hypertrophy. His complete series of twenty-seven hypertensive hearts shows an L/R ratio of 1.97, while our group of ten gives an average of 2.704.

#### SUMMARY

Sixty-four human hearts were divided and weighed according to the method described by Herrmann. These included normal hearts, hearts from persons dead of some form of wasting disease, hypertensive hearts, hearts from persons dead of rheumatic disease and hearts from persons dead of cardiovascular syphilis, with involvement of the aortic valves and without such change.

## CONCLUSIONS

1. In patients dying of wasting disease, the heart weight decreases slightly less than that of the body in general.
2. In patients with rheumatic deformity of the mitral valve alone, the increase in heart weight is due to an increase in the weight of the right ventricle and the auricles.
3. In large hearts associated with regurgitation at the aortic valves, rheumatic or syphilitic, the entire heart hypertrophies, but the greatest increase is in the left ventricle. The assumption that only the left ventricle shows definite hypertrophy in cases of syphilitic aortic regurgitation of some duration is not acceptable.
4. In the production of cardiac hypertrophy, mechanical factors are not solely effective. The figures for the large syphilitic hearts show diffuse cardiac hypertrophy whether or not aortic regurgitation was present.
5. The hypertensive hearts without valvular disease do not equal in size the hearts in which long-standing valvular defects at the aortic orifice are found. In the hypertensive type, however, the proportionate increase in the size of the left ventricle is greater than in other groups.
6. A comparison of our work with that of Herrmann shows that the L/R ratio in man is greater than that in the dog: The ratio of total ventricular weight to body weight is twice as great in the dog as in man.
7. The customary method of determining the thickness of the ventricular walls at autopsy is apt to mislead as to the presence of right ventricular hypertrophy, which may be overlooked.
8. The results obtained by the method here employed and those obtained by Lewis with his method are similar for normal hearts and hearts with syphilitic lesions; they are approximately alike for hearts with rheumatic valvular deformity. In the hypertensive and nephritic groups, the results obtained by the two methods do not agree.

# CLINICAL STUDIES OF RESPIRATION

## III. INFLUENCE ON THE EXPIRATORY POSITION OF THE CHEST IN MAN OF AN INSPIRED AIR WHICH IS LOW IN OXYGEN AND HIGH IN CARBON DIOXIDE, AND OF RESISTANCE TO INSPIRATION AND TO EXPIRATION

J. A. GREENE, M.D.

IOWA CITY

In one previous study,<sup>1</sup> it was found that the expiratory position of the chest may be increased by slight muscular work, and in another,<sup>2</sup> evidence was presented which indicated that this alteration may be produced by a psychic or reflex mechanism. One purpose of this study was to determine whether or not anoxemia or the accumulation of carbon dioxide would alter the expiratory position of the chest.

In a previous study,<sup>2</sup> the carbon dioxide excreted was determined by the passage of dry expired air through weighed containers of soda lime and calcium chloride. This offered a slight resistance to expiration. Since Bittorf and Forschbach<sup>3</sup> and Siebeck<sup>4</sup> showed that stenosis of extrinsic air passages increased the middle position of the chest, it was decided to determine the influence of a constant resistance to expiration and to inspiration of the expiratory position of the chest.

### METHOD

All subjects were accustomed to the apparatus and had had their basal metabolic rates determined several times before. In order to exclude the psychic factor as much as possible, the subjects were not

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From the Lily Laboratory for Clinical Research, Indianapolis City Hospital, and Indiana University School of Medicine.

1. Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respiration: I. A Plethysmographic Study of Quiet Breathing and the Influence of Some Ordinary Activities on the Expiratory Position of the Chest in Man, *Arch. Int. Med.* **52**:44 (July) 1933.

2. Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respiration: II. The Influence of the Determination of the Basal Metabolism on the Respiratory Movements in Man, and the Effect of These Alterations on the Calculated Basal Metabolic Rate, *Arch. Int. Med.* **52**:226 (Aug.) 1933.

3. Bittorf, A., and Forschbach, J.: Investigation on the Lung Filling up in Sickness, *Ztschr. f. klin. Med.* **70**:474, 1910.

4. Siebeck, R.: On the Influence of the Respiratory Mechanism Through Diseased Conditions of Respiration and Circulation, *Deutsches Arch. f. klin. Med.* **100**:205, 1910.

informed that the composition of the inhaled gas differed from that of air. The psychic factor could not be excluded in the experiments in cases in which there was resistance to the respirations.

A record of the respirations was obtained by means of the body plethysmograph,<sup>1</sup> with the subject in the supine position. After the expiratory position had been practically constant for from five to ten minutes, the subject was connected to the ordinary spirometer used in

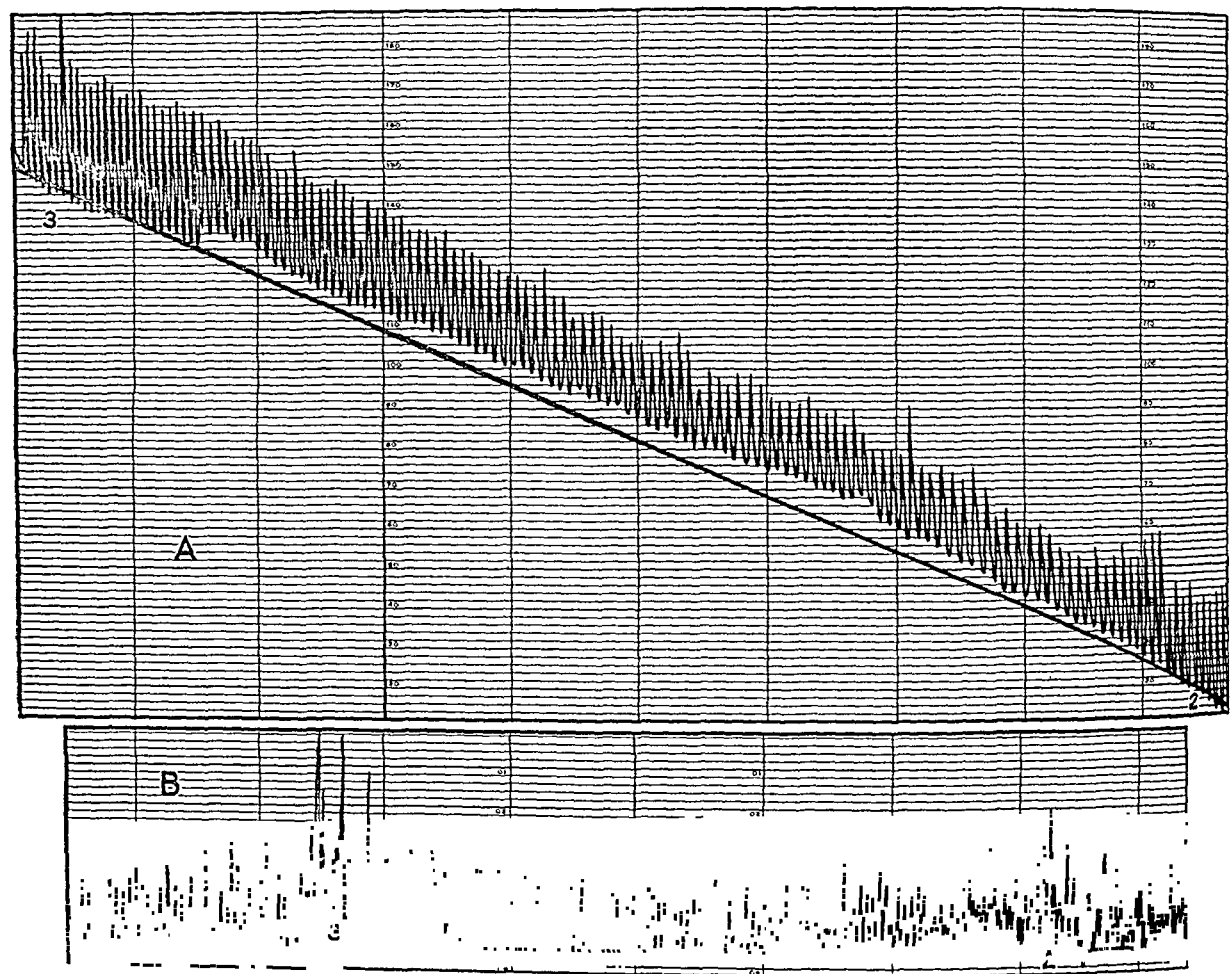


Chart 1.—In this and subsequent charts the graphs are read from right to left, and the down stroke represents expiration. *A* is a spirogram taken simultaneously with the plethysmogram, *B*. At 1 the mouth-piece was inserted; at 2 the nose-clip was applied and the spirographic record begun, and at 3 the spirographic record was discontinued. In this chart it is shown that no alteration in the expiratory position occurred when the oxygen was 5.2 per cent.

determining the basal metabolism. For the experiments on anoxemia the spirometer was filled with the air of the room, and the carbon dioxide was removed in the usual way. When the effect of carbon dioxide was studied, the spirometer was filled with oxygen, and an empty con-

tainer of the type used for the soda lime was employed. The rate and amplitude of respirations were watched, and in most cases the subject was disconnected from the spirometer at about the time he became conscious of increased breathing. Samples of air were removed from

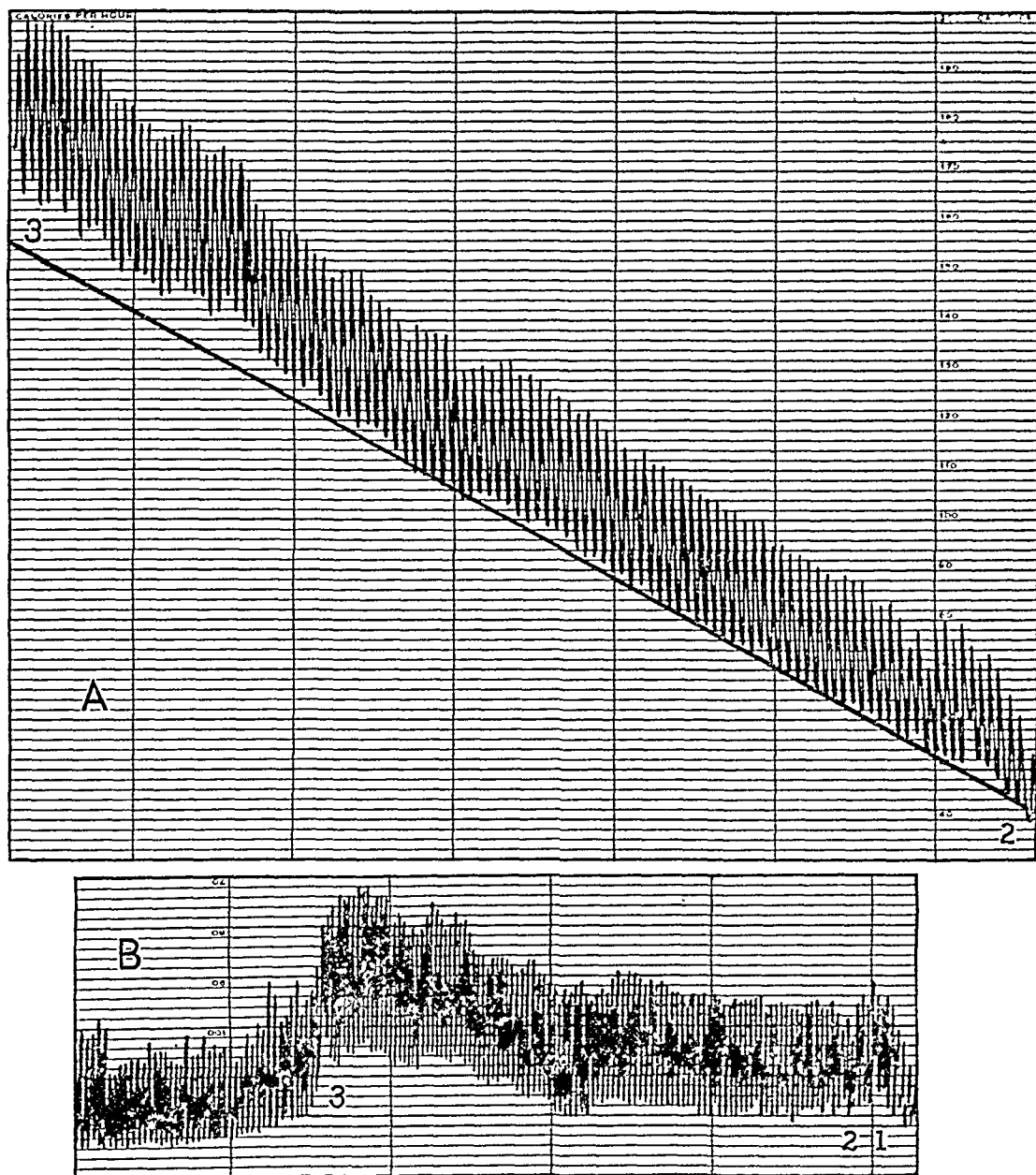


Chart 2.—An increase in the expiratory position occurred when the oxygen was 11 per cent.

the spirometer and analyzed by the Henderson apparatus for the analysis of gas.

When the effect of resistance to inspiration and to expiration was studied, the spirometer was filled with oxygen, and the carbon dioxide was removed in the usual way. Resistance to expiration was produced

by placing weights on the spirometer bell, and resistance to inspiration by placing weights on the counterbalance of the spirometer.

### RESULTS

The influence of anoxemia on the expiratory position of the chest was determined in six subjects. In five of them the expiratory position remained practically constant when the oxygen had decreased to about 7, 6, 6, 5.2 and 8 per cent. In one subject it increased slightly when the oxygen was 11 per cent. The two reactions are shown in charts 1 and 2. The graphs are read from right to left, and the down stroke is expiration. In each chart, *A* is a spirogram taken simultaneously with the plethysmogram *B*. At 1 the mouthpiece was inserted, at 2 the nose-clip was applied and the spirographic record begun, and at 3 the spirographic record was discontinued. Chart 1 shows no alteration of the expiratory position when the oxygen was 5.2 per cent,

#### *Influence of Simultaneous Anoxemia and Increase in Carbon Dioxide in Four Subjects*

Subject	Test	Carbon Dioxide in the Inspired Air, per Cent	Oxygen in the Inspired Air, per Cent	Change in Expiratory Position
1	1	5.2	15.0	Slight increase
2	1	4.7	13.0	Slight increase
3	1	6.1	17.0	No change
4	1	6.3	16.0	No change
	2	6.6	10.0	No change

and chart 2 shows an increase in the expiratory position when the oxygen was 11 per cent.

Three of the five subjects in whom the influence of carbon dioxide was studied showed no alteration of the expiratory position of the chest when the carbon dioxide had increased to 7.2, 6 and 7.8 per cent. In two subjects the expiratory position increased slightly with 4 and 7.3 per cent carbon dioxide. The increase was less than that shown in chart 2.

Since marked anoxemia or accumulation of carbon dioxide acting separately produced little or no alteration of the expiratory position of the chest, the influence of simultaneous anoxemia and increase in carbon dioxide was studied in four subjects. The results are shown in the table.

The increase in the expiratory position in subjects 1 and 2 was less than that shown in chart 2.

The application of weights of 0.3, 0.6 and 1 pound (0.15, 0.3 and 0.5 Kg.) to the spirometer bell or to the counterbalance produced no

alteration of the expiratory position of the chest in any subject. When a weight of 2 pounds (0.9 Kg.) was applied to the counterbalance as resistance to inspiration, there was only a slight decrease in the expiratory position, as shown in chart 3. The weight was applied to the counterbalance at 1 and was removed at 2. *B* shows the slight effect

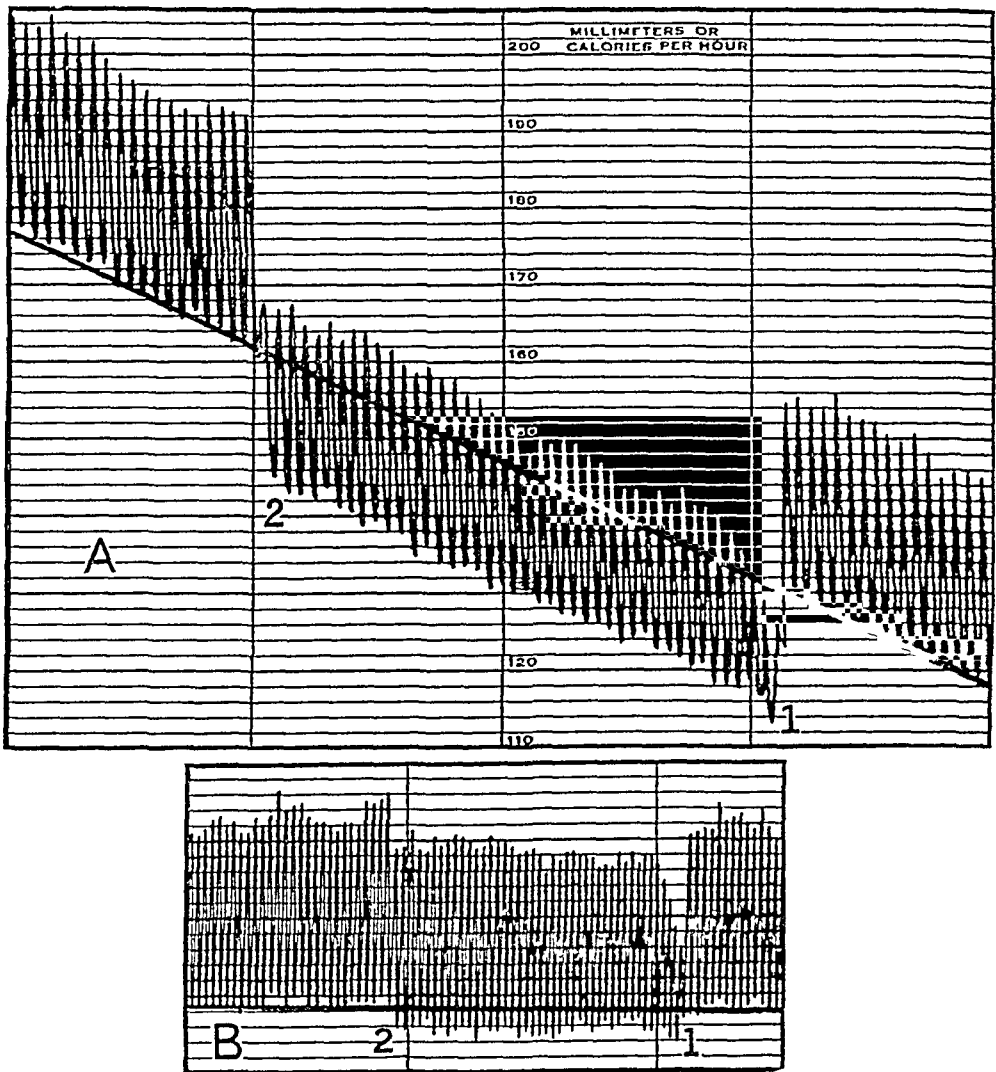


Chart 3.—Only a slight decrease in the expiratory position occurred when a weight of 0.9 Kg. was applied to the counterbalance as resistance to inspiration.

on the expiratory position of the chest, while *A* shows a greater effect due to expansion of the air in the spirometer system.

When the 2-pound (0.9 Kg.) weight was placed on the spirometer bell to produce resistance to expiration, the expiratory position was increased from 250 to 500 cc. in all subjects. This increase occurred immediately after the resistance was applied. The first expiration was short, followed by a greater inspiration. After the initial increase,



the expiratory position decreased slightly in four subjects, and had returned to its previous level in one subject before the resistance was removed. The effect is shown in chart 4. The weight was applied

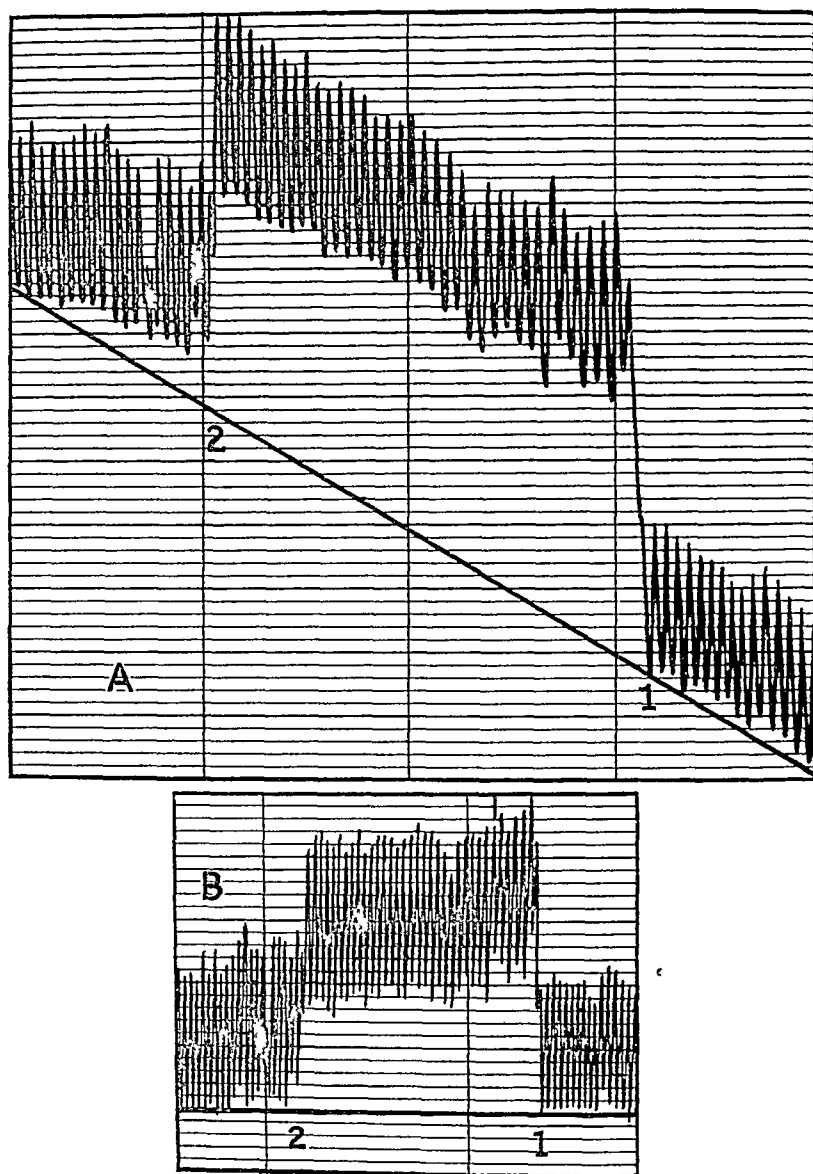


Chart 4.—When a weight of 0.9 Kg. was placed on the spirometer bell to produce resistance to expiration, the expiratory position was increased from 250 to 500 cc. in all subjects.

to the top of the spirometer bell for resistance to expiration at 1 and was removed at 2. The increase in the expiratory position is shown in B, while the effect shown in A is exaggerated, owing to the compression of the air in the spirometer system.

## COMMENT

The influence of carbon dioxide and anoxemia on the rate and amplitude of the respirations has been studied by numerous investigators. Bohr,<sup>5</sup> Bittorf and Forschbach<sup>3</sup> and Siebeck<sup>4</sup> studied the effect on the middle position of the chest of an increase of carbon dioxide and a decrease of oxygen in the inspired air. The increase in the middle position of the chest reported by these investigators indicates, at first glance, that the expiratory position of the chest must have increased. But the middle position of the chest, which is defined as the position of the chest half way between inspiration and expiration, may be increased with an increase either in amplitude or in expiratory position, or in both. In these experiments, the middle position of the chest was altered during each experiment, but in the experiments on the accumulation of carbon dioxide and anoxemia, it was usually increased by an increase of amplitude alone.

These results indicate that the accumulation of carbon dioxide, the anoxemia and the resistance to the respirations are not entirely responsible for the alteration of the expiratory position of the chest that may occur during slight muscular work or during the determination of the basal metabolism.

## SUMMARY

1. The expiratory position of the chest may or may not be altered by either a decrease in oxygen or an increase in carbon dioxide, or by both, in the inspired air.

2. A great resistance to expiration was necessary to alter the expiratory position of the chest in normal subjects, while the same resistance to inspiration produced little or no change.

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5. Bohr, C.: The Functional Variation in the Middle Position and Vital Capacity of the Lung: Normal and Pathologic Emphysema, *Deutsches Arch. f. klin. Med.* **88**:385, 1906-1907.

# CLINICAL STUDIES OF RESPIRATION

## IV. SOME OBSERVATIONS ON CHEYNE-STOKES RESPIRATION

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The periodic irregularity of respiration, characterized by a period of apnea followed by breathing that begins almost imperceptibly, waxes until it becomes dyspneic and then wanes until apnea follows the last shallow breath, was first described by Cheyne, in 1818, and later by Stokes, in 1854.

This type of breathing was considered pathologic by the earlier investigators, but Mosso<sup>1</sup> described Cheyne-Stokes respiration in the hibernating dormouse, and in man during sleep and after the administration of chloral. Pembrey<sup>2</sup> confirmed the finding of Cheyne-Stokes breathing in hibernating animals, and showed that the administration of carbon dioxide would abolish the irregularity. Pembrey and Allen<sup>3</sup> had previously shown that the administration of oxygen, carbon dioxide or gas deficient in oxygen abolished Cheyne-Stokes breathing in a patient and explained the phenomenon by a diminished excitability of the nervous system; the carbon dioxide accumulates and the oxygen diminishes until the nerve cells are stimulated; then respirations begin. During the hyperpnea, the carbon dioxide is washed out, and sufficient oxygen is taken in. Apnea follows because of lack of sufficient carbon dioxide to stimulate the nerve cells.

Cheyne-Stokes respiration may occur in several pathologic conditions, tumors of the brain, cerebral hemorrhage, meningitis, fractured skull, cardiac failure, uremia and arteriosclerosis. It has been produced experimentally in animals by Eyster<sup>4</sup> and others by increasing the intracranial pressure and by Roberts<sup>5</sup> when he administered epinephrine intravenously to rabbits and cats under ethyl carbamate (urethane)

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From the Lilly Laboratory of Clinical Research and the Indiana University School of Medicine.

1. Mosso, A.: *Arch. per le sc. med.* **2**:442, 1878; *Arch. f. Physiol. (supp.)*, 1886, p. 37. Quoted by Pembrey.<sup>2</sup>

2. Pembrey, M. S.: *Observations on Cheyne-Stokes Respiration*, *J. Path. & Bact.* **12**:258, 1908.

3. Pembrey, M. S., and Allen, R. W.: *Observations upon Cheyne-Stokes Respiration*, *J. Physiol.* **32**:XVIII, 1905.

4. Eyster, J. A. E.: *Clinical and Experimental Observations upon Cheyne-Stokes Respiration*, *J. Exper. Med.* **8**:565, 1906.

5. Roberts, F.: *Cheyne-Stokes Respiration: I. Production by Adrenalin*, *J. Physiol.* **56**:101, 1922.

and a chloroform and ether mixture anesthesia. Greeley and Greeley<sup>6</sup> produced it by partial obstruction of the cerebral blood vessels. Swindle<sup>7</sup> was able to train anesthetized dogs and cats to breathe in a Cheyne-Stokes fashion, and later showed that decapitation of the muskrat and sea-lion scarcely altered their normal periodic breathing. MacLeod<sup>8</sup> produced Cheyne-Stokes breathing in decerebrated cats by periodic compression of the vertebral arteries, and by making the animals breathe through long tubes and a small flask of soda lime that removed the carbon dioxide. This method was the same as that used by Douglas and Haldane<sup>9</sup> to produce Cheyne-Stokes breathing in man.

Eyster<sup>4</sup> was the first to differentiate between different types of Cheyne-Stokes breathing by the relation of the breathing to changes in blood pressure. In cases in which the irregularity occurred with increased intracranial pressure, he found that the blood pressure fell during the apnea and increased with the hyperpnea, while in cases of cardiac failure and nephritis the blood pressure rose with an increase in the pulse rate during the apnea and fell with a decrease in the pulse rate during the hyperpnea. This was the first method available for differentiating between the different types of Cheyne-Stokes respiration other than by the pathologic conditions in which it occurred.

A body plethysmograph has recently been described<sup>10</sup> that records the ventilation of the lungs with a certain degree of accuracy and without interference with the breathing. Conner and Stillman<sup>11</sup> showed that the thoracic wall and diaphragm do not always have the same type or degree of action in disturbed respirations; it appeared that the body-plethysmograph might be of aid in the study of some of the abnormalities of respiration.

Plethysmographic records were obtained of the breathing of twenty patients with Cheyne-Stokes respiration. With some patients only one

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6. Greeley, P. O., and Greeley, C. E.: Circulatory Changes During Periodic Breathing Produced by Moderate Obstruction to the Cerebral Arteries, *Am. J. Physiol.* **95**:371 (Nov.) 1930.

7. Swindle, P. F.: Superimposed Respirations or Cheyne-Stokes Breathing of Amphibious and Nonamphibious Mammals, *Am. J. Physiol.* **79**:188, 1926.

8. MacLeod, J. J. R.: Periodic Breathing and the Effects of Oxygen Administration in Decerebrate Cats, *Am. J. Physiol.* **55**:175, 1921.

9. Douglas, C. G., and Haldane, J. S.: The Causes of Periodic or Cheyne-Stokes Breathing, *J. Physiol.* **38**:401 (June) 1909.

10. Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respirations: I. A Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities upon the Expiratory Position of the Chest in Man, *Arch. Int. Med.* **52**:44 (July) 1933.

11. Conner, L. A., and Stillman, R. G.: A Pneumographic Study of Respiratory Irregularities in Meningitis, *Tr. A. Am. Physicians* **26**:464, 1911.

tracing was obtained, while with other patients tracings have been taken at various intervals.

According to these records, Cheyne-Stokes respirations can be divided into two groups. One group is associated with cerebral lesions and is characterized by an almost constant expiratory position, as shown in graph *A* of chart 1, while the other group occurs in association with cardiovascular disease and exhibits a fluctuating expiratory position, as

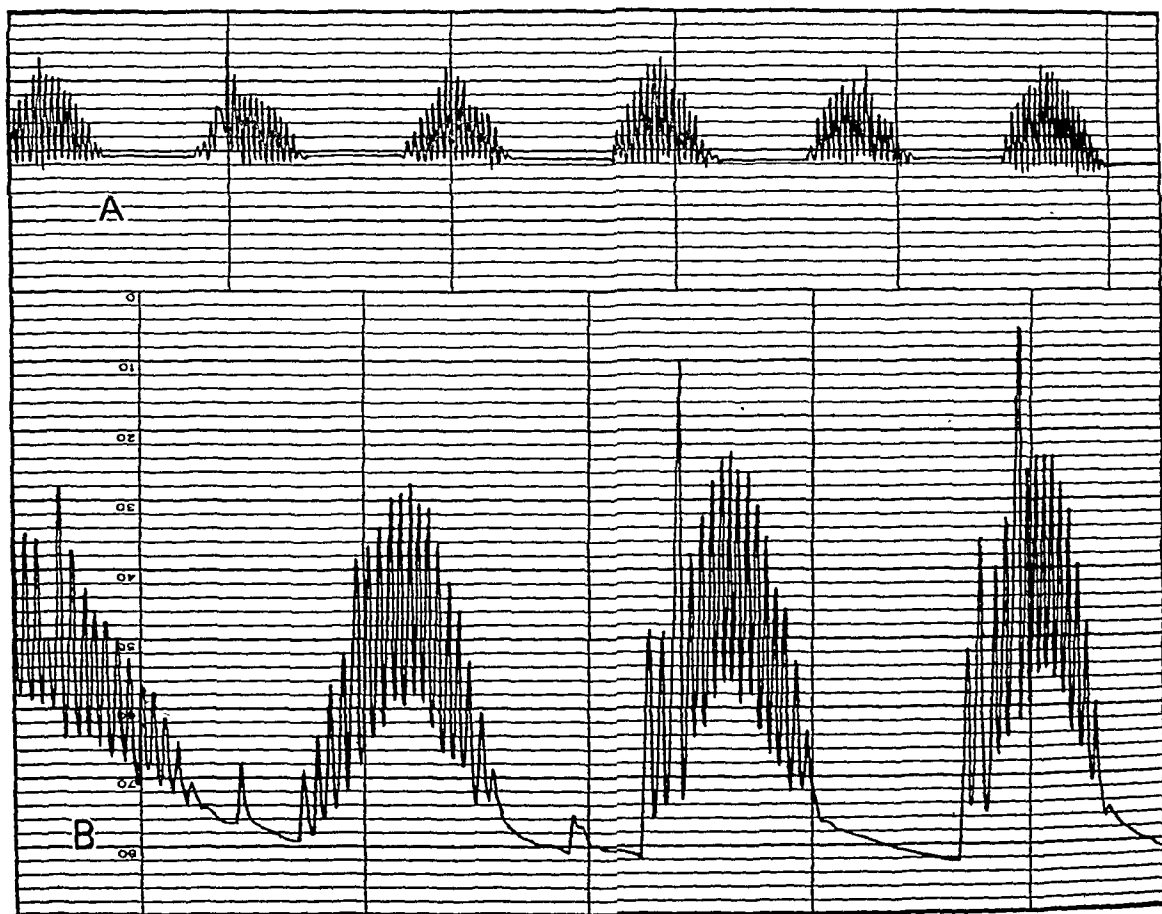


Chart 1.—The two different types of Cheyne-Stokes respirations. *A*, which exemplifies the group associated with cerebral lesions, is characterized by an almost constant expiratory position; *B*, which exemplifies the group associated with cardiovascular diseases, shows a fluctuating expiratory position. The graphs are read from left to right. The down stroke represents expiration.

shown in graph *B* of chart 1. The graphs are read from left to right, and the down stroke represents expiration.

In the cerebral group only the Cheyne-Stokes respiration in cases of cerebral hemorrhage and fracture of the skull was studied. In the cardiovascular group, the respiration in cases of hypertensive heart disease, arteriosclerotic heart disease and syphilitic heart disease (aortic insufficiency with myocardial failure) was studied, but no

cases of arteriosclerosis without cardiac impairment or uremia were observed. This grouping of Cheyne-Stokes respirations coincides with Eyster's.<sup>4</sup>

The degree of alteration of the expiratory position of the chest in the second group varies with different cases from 250 cc. to 1,000 cc. of air and can be detected clinically if one places the eye near the level of the anterior surface of the body and focuses during the apnea on a point only slightly above the patient's abdomen and chest. With the occurrence of hyperpnea, the increase in the expiratory position can be detected by a rise in the chest and, more clearly, by a rise in the abdomen.

Pembrey and Allen<sup>3</sup> were able to change the Cheyne-Stokes respiration of a patient to regular breathing by the administration of oxygen, air deficient in oxygen or air containing an excess of carbon dioxide. Anthony, Cohn and Steele<sup>12</sup> were able to abolish the irregularity of Cheyne-Stokes respiration by increasing the carbon dioxide in the inhaled air, but the irregularity persisted when the oxygen was increased. The reaction of the patients in my series to the administration of oxygen further supported the classification into two groups. The respiration gradually became regular when oxygen was administered to two patients who exhibited a constant expiratory position, as shown in chart 2. The graph is read from left to right, and the down stroke represents expiration. Oxygen was administered at 1 and continued throughout the graph. When oxygen was discontinued, the Cheyne-Stokes respiration recurred.

The respiration of the other group with fluctuating expiratory position either was unaltered or showed a prolongation of the apnea and a decrease of the hyperpnea when oxygen was given, as shown in chart 3. The graph is read from left to right, and the down stroke represents expiration. Oxygen was administered at 1 and continued throughout the graph.

When 5 per cent carbon dioxide was added to the oxygen given to the patients with cardiac involvement, the respiration became regular and the expiratory position was elevated, as shown in chart 4. The graph is read from left to right, and the down stroke represents expiration. Five per cent carbon dioxide was begun at 1 and discontinued at 2.

These findings indicate that in the cerebral group the deficiency in oxygen played a prominent rôle, while in the cardiac group the mechanism appeared more complex.

Since carbon dioxide is a respiratory stimulant and abolishes the irregularity in the cardiac group of Cheyne-Stokes respirations, caffeine

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12. Anthony, A. J.; Cohn, A. E., and Steele, J. M.: Studies on Cheyne-Stokes Respiration, *J. Clin. Investigation* **11**:1321 (Nov.) 1932.

was given to some of the patients with this type of breathing. The irregularity disappeared, but only after comparatively large doses of caffeine had been given, and then the breathing was not regular, but more of Biot's type, as shown in chart 5. The graph is read from left to right, and the down stroke represents expiration. This patient had typical Cheyne-Stokes respiration of the type shown in chart 1, graph B, before medication with caffeine, and the Cheyne-Stokes breathing returned after the caffeine was discontinued.

In the light of the aforementioned findings, the generally accepted explanation of Cheyne-Stokes respiration appears intelligible when

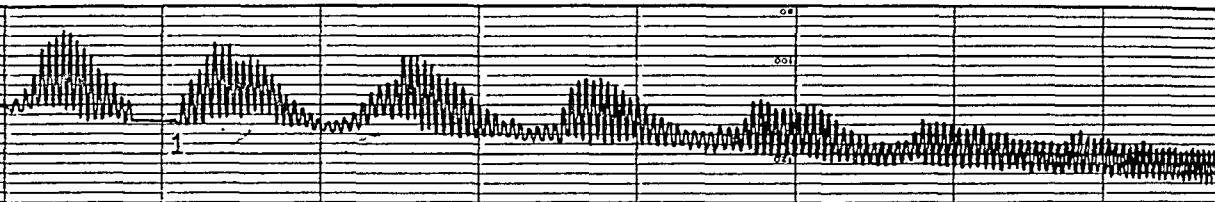


Chart 2.—The gradual change of Cheyne-Stokes respiration to regular breathing when oxygen was administered (at 1) to a patient who exhibited a constant expiratory position.

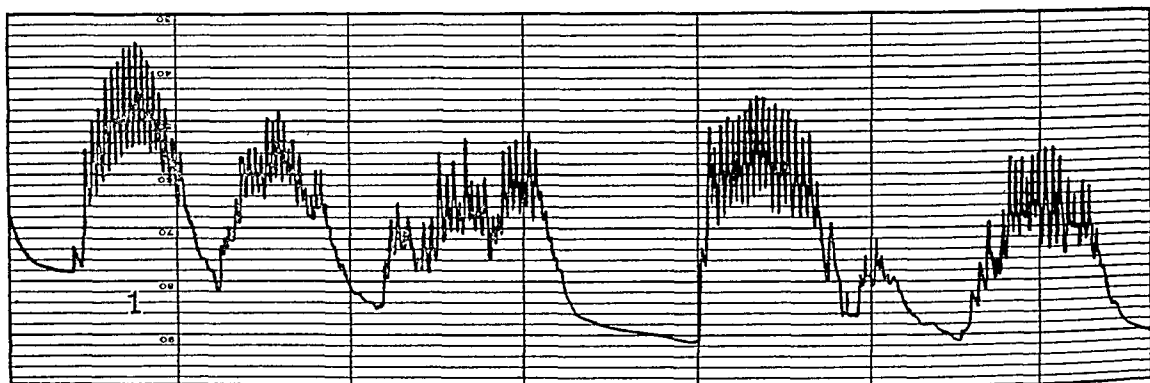


Chart 3.—When oxygen was given (at 1) to a patient with a fluctuating expiratory position, the respirations were either unaltered or showed a prolongation of the apnea and a decrease of the hyperpnea.

applied to the cerebral group, but is not so clear when applied to the cardiac group on which oxygen either had no effect or had the effect of prolonging the apnea.

The relation of the circulation of the brain to the production of Cheyne-Stokes respiration was shown by Eyster,<sup>4</sup> but in the light of more recent work his explanation of the mechanism of production does not seem clear. His explanation of the production of apnea by anemia of the respiratory center, however, is supported by the work of Greeley and Greeley.<sup>6</sup> Roberts<sup>5</sup> was able to produce Cheyne-Stokes respiration

in the cat by intravenous injection of epinephrine, and explained this type of breathing by anemia of the respiratory center. There were waves of increased and decreased blood pressure which he thought caused the anemia of the respiratory center by vasoconstriction. However, Wright<sup>13</sup> did not find any apnea in a decerebrated animal with anemia of the respiratory center, and epinephrine did not produce

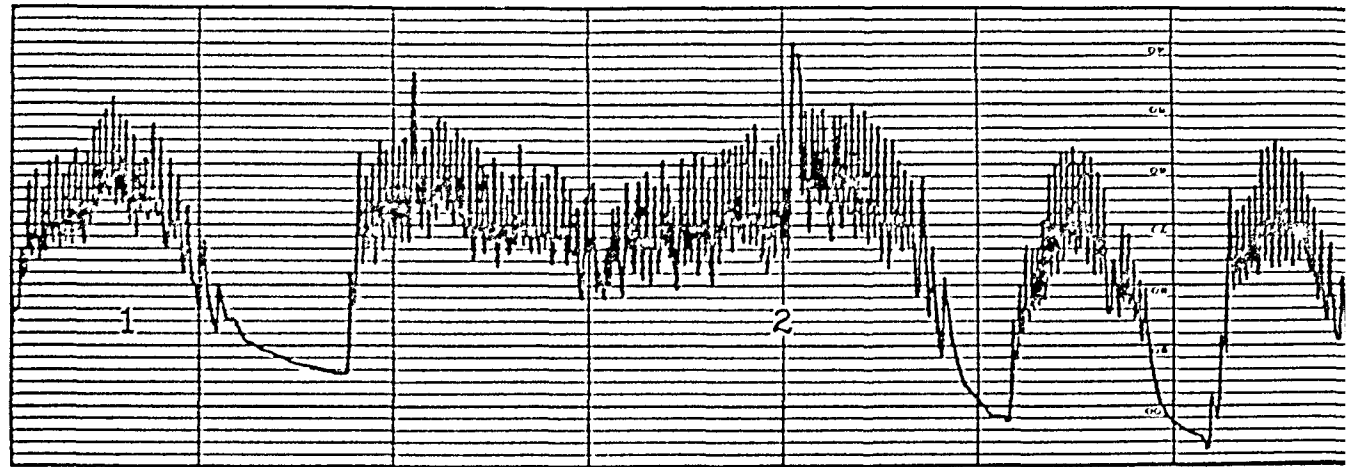


Chart 4.—The respirations of a patient with cardiac involvement became regular and the expiratory position was elevated when 5 per cent carbon dioxide was added to the oxygen administered.

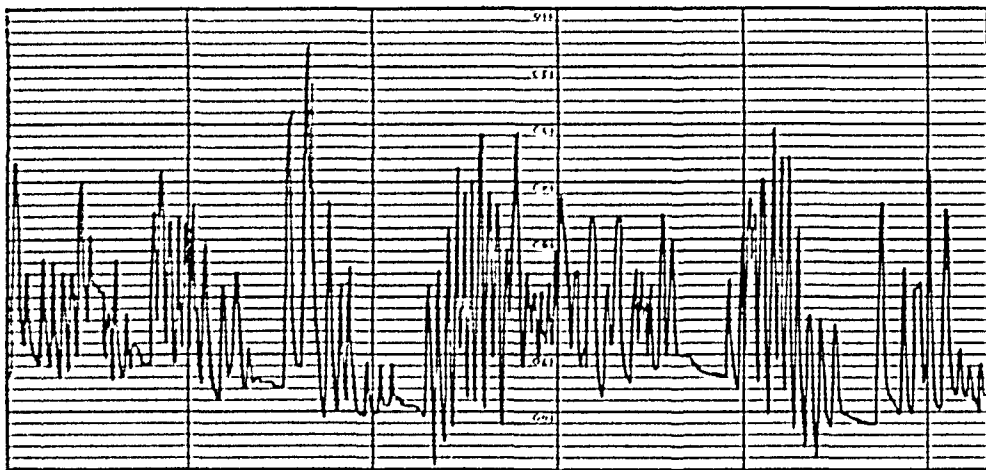


Chart 5.—The effects of the administration of caffeine on the Cheyne-Stokes respiration of a patient with cardiac disease; the irregularity disappeared, but only after comparatively large doses had been given, and then the respiration was of Biot's type.

apnea when the vagi were cut and the carotid bulbs were denervated. Wright also found that epinephrine did not produce apnea if the

13. Wright, S.: Action of Adrenalin and Related Substances on Respiration, *J. Physiol.* 69:493 (June) 1930.



increase in blood pressure was prevented by a compensatory apparatus connected to the abdominal aorta, but apnea occurred if the blood pressure was permitted to increase. Heymans and Bouckaert<sup>14</sup> also showed the relation of the carotid bulb reflex to epinephrine-induced apnea.

Scott<sup>15</sup> found that stimulation of the vagus produced apnea even at the height of hyperpnea, and Mellanby and Huggett<sup>16</sup> found that the injection of epinephrine also produced apnea even in the midst of hyperpnea from an increase of carbon dioxide or a deficiency of oxygen. The apnea developed by a waning of the respirations.

The importance of the reflex control of respirations has become more prominent. Bohr<sup>17</sup> found that work increased the middle position of the chest and thought that the increase in position was a compensatory mechanism to widen the pulmonary capillaries, while Bittorff and Forschbach<sup>18</sup> showed that it was a reflex phenomenon that at times was detrimental to the proper gaseous exchange. An increase in the expiratory position of the chest through a reflex mechanism that was detrimental to the proper gaseous exchange has also been demonstrated by Greene and Coggeshall.<sup>19</sup> Harrison, Calhoun, Cullen, Wilkins and Pilcher<sup>20</sup> showed that the chemical factor is not sufficient to cause the dyspnea in patients with cardiac disease, and that in dogs in which the vital capacity had been reduced the tachypnea was due to a reflex mechanism and not to chemical factors. Harrison, Harrison, Calhoun and Marsh<sup>21</sup> showed that passive movements of the extremity

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14. Heymans, C., and Bouckaert, J. J.: Sinus Caroticus and Respiratory Reflexes: I. Cerebral Flow and Respiration, *J. Physiol.* **69**:254 (April) 1930.

15. Scott, F. H.: On the Relative Parts Played by Nervous and Chemical Factors in the Regulation of Respiration, *J. Physiol.* **37**:301, 1908.

16. Mellanby, J., and Huggett, A. St. G.: The Adrenalin and Vagal Types of Apnea, *J. Physiol.* **57**:395 (Aug.) 1923.

17. Bohr, C.: The Functional Variations of the Middle Position and Vital Capacity of the Lungs: Normal and Pathological Emphysema, *Deutsches Arch. f. klin. Med.* **88**:385, 1906-07.

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of the dog increased the ventilation whether or not the circulation to and from the moving part was intact. The effect was abolished by interference with the nerve supply.

Bass<sup>22</sup> studied the influence of stenosis of the extrinsic air passages on subjects before and after administration of atropine, and concluded that the middle position of the chest is controlled through the vagus nerve. Herzog<sup>23</sup> concluded that the varying carbon dioxide content of the expired air was a consequence and not the cause of Cheyne-Stokes breathing. He placed the responsibility on impulses carried by the vagus nerve.

Meakins<sup>24</sup> recognized the inadequacy of the explanation of Cheyne-Stokes respiration by anoxemia and carbon dioxide, and used the explanation of unequal ventilation of the lungs as the auxiliary mechanism. Haldane, Meakins and Priestley<sup>25</sup> had previously had to resort to this explanation as the cause of anoxemia in the effort syndrome.

The reflex action on the respirations is evidently complicated, to judge by the work of Hertzman and Gesell,<sup>26</sup> Moore,<sup>27</sup> Scott,<sup>15</sup> Wright,<sup>13</sup> Heymans and Bouckaert<sup>14</sup> and Harrison and others.<sup>21</sup> Lumsden<sup>28</sup> has also postulated from his findings that there is a series of respiratory centers in the lower brain stem, each of which is released if the center above is destroyed, and that the mechanism of quiet breathing depends on an interaction between these centers. From work on amphibious and nonamphibious mammals, Swindle<sup>7</sup> concluded that there were rudimentary respiratory centers in the spinal cord of mammals. Trevan and Boock<sup>29</sup> suggested from their work with the cat that the part of the respiratory center that remains after decerebration just behind the anterior edge of the pons depends more on vagal than on chemical stimuli.

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An undulatory type of breathing that may occur in normal persons has been described by Mosso,<sup>30</sup> Conner and Stillman<sup>11</sup> and Greene and Coggeshall.<sup>10</sup> In this undulatory type of breathing there is a rhythmical alteration of the expiratory position of the chest with variations of amplitude of breathing. Conner and Stillman<sup>11</sup> thought that all patients with Cheyne-Stokes respiration passed through this undulatory stage. A similar type of breathing, but with more exaggerated fluctuations of the expiratory position and amplitude, is sometimes seen in patients before Cheyne-Stokes breathing begins, when the breathing is becoming regular, or when a patient with frank Cheyne-Stokes respiration has his attention directed to his breathing. The expiratory position of the chest is altered, but there is no apnea, as shown in chart 6. The graph is read from left to right, and the down stroke represents expiration.

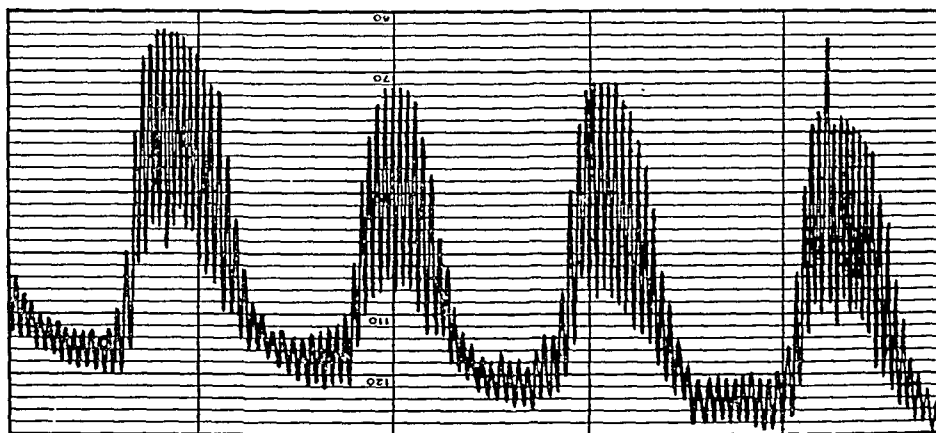


Chart 6.—A type of breathing which sometimes occurs before Cheyne-Stokes breathing begins or when it is becoming regular; the fluctuations of the expiratory position and the amplitude are more exaggerated than in normal undulatory breathing.

It appears not unlikely that the undulatory type of breathing that occurs in the normal person is due to an interaction on the respirations of reflexes different from those that occur in persons with regular breathing. This is supported by the finding of Mosso<sup>30</sup> and Conner and Stillman<sup>11</sup> that it occurs more frequently in the young and the aged. The similarity of the undulatory breathing to the Cheyne-Stokes breathing of the cardiovascular group suggests that a similar reflex mechanism plays a prominent part in the production of this type of Cheyne-Stokes breathing. This idea is further supported by: (1) the physiologic occurrence of the Cheyne-Stokes type of breathing in certain animals, (2) the occasional presence of it in infants and elderly people, (3) the reaction of patients with this type of Cheyne-Stokes respiration

30. Mosso: Les mouvements respiratoires du thorax et du diaphragme, Arch. ital. de biol. 40:43, 1903; quoted by Conner and Stillman.<sup>11</sup>

to the administration of oxygen, (4) their reaction to respiratory stimulants, as carbon dioxide and caffeine, (5) the fact that the irregularity is frequently abolished when the patient's attention is directed to his breathing and (6) the fact that the expiratory position of the chest of normal persons was not materially altered when the inspired air was changed by an increase of carbon dioxide, by a decrease of oxygen or by a simultaneous decrease of oxygen and increase of carbon dioxide.<sup>31</sup>

#### SUMMARY

1. Records of the respirations of twenty patients with Cheyne-Stokes breathing have been obtained by a body plethysmograph.

2. Cheyne-Stokes' respirations are divided into two groups: In one group the expiratory position of the chest is practically constant; in the other it fluctuates markedly.

3. The response of these patients to the administration of oxygen further supports the classification into two groups.

4. The fluctuations of the expiratory position of the chest in the second group can be detected clinically in most instances.

5. It is suggested that a reflex mechanism may play a prominent rôle in the production of the Cheyne-Stokes breathing in the group with the fluctuating expiratory position.

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# EFFECT ON IDIOPATHIC HYPOCHROMIC ANEMIA OF BEEF STEAK (HAMBURGER STEAK) DIGESTED WITH NORMAL GASTRIC JUICE

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The reports of cases of idiopathic hypochromic anemia continue to increase, but controversy exists, nevertheless, as to whether or not this condition can be accepted as a clinical entity. Some authors<sup>1</sup> think of this anemia as an atypical form of pernicious anemia. Others consider that it is a form of anemia resulting from undiscovered chronic loss of blood. Opinions<sup>2</sup> have been expressed that the anemia is the result of dietary deficiencies or that it is related to chlorosis, once so common in young girls. The view most generally held, however, is that the anemia and the clinical picture are the result of some deficiency in gastric secretion<sup>3</sup> or the consequence of an inability of the gastrointestinal tract to absorb from the food substances necessary for the formation of blood.<sup>4</sup>

In 1929, Castle<sup>5</sup> showed that when beef steak properly digested with normal gastric juice was fed to patients suffering from pernicious anemia, a remission in the disease was produced similar to that resulting from treatment of the patients with liver. The experiments reported in this paper were based entirely on Castle's work, and represent an effort to determine whether or not patients with idio-

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1. Dameshek, W.: Primary Hypochromic Anemia, *Am. J. M. Sc.* **182**:520, 1931. Witts, L. J.: Simple Achlorhydric Anemia, *Guy's Hosp. Rep.* **80**:253, 1930.

2. Bloomfield, A. L.: Relations Between Primary Hypochromic Anemia and Chlorosis, *Arch. Int. Med.* **50**:328 (Aug.) 1932.

3. Waugh, T. R.: Hypochromic Anemia with Achlorhydria, *Arch. Int. Med.* **47**:71 (Jan.) 1931. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastro-Duodenal Contents in Certain Cases of Anemia, *Am. J. M. Sc.* **181**:25, 1931.

4. Haden, R. L.: Simple Achlorhydric Anemia, *J. A. M. A.* **99**:1398 (Oct. 22) 1932. Wintrobe, M. M., and Beebe, R. T.: Idiopathic Hypochromic Anemia, *Medicine* **12**:187, 1933.

5. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am. J. M. Sc.* **178**:748, 1929.

pathic hypochromic anemia would likewise respond favorably if given beef steak digested in normal gastric juice. Such tests, it was believed, would serve to indicate whether the same or another intrinsic factor is lacking in the gastric secretion of these patients and might add further information in the comparison of this type of anemia with pernicious anemia.

Five cases of idiopathic hypochromic anemia have been selected. The procedures followed in each instance will be discussed briefly.

TABLE 1 (CASE 1).—*Results of the Examination of the Blood*

	On Admission	On Discharge
Red blood count.....	4,100,000	5,260,000
Hemoglobin .....	6 Gm. (41%)	15.1 Gm. (101%)
Volume of packed red cells.....	21.2 per cent	44.2 per cent
Mean corpuscular volume.....	59 cubic microns	84 cubic microns
Mean corpuscular hemoglobin.....	15 micromicrograms	29 micromicrograms
Mean corpuscular hemoglobin concentration.....	25 per cent	34 per cent
Reticulocytes .....	1.4 per cent	
White blood count.....	6,100	

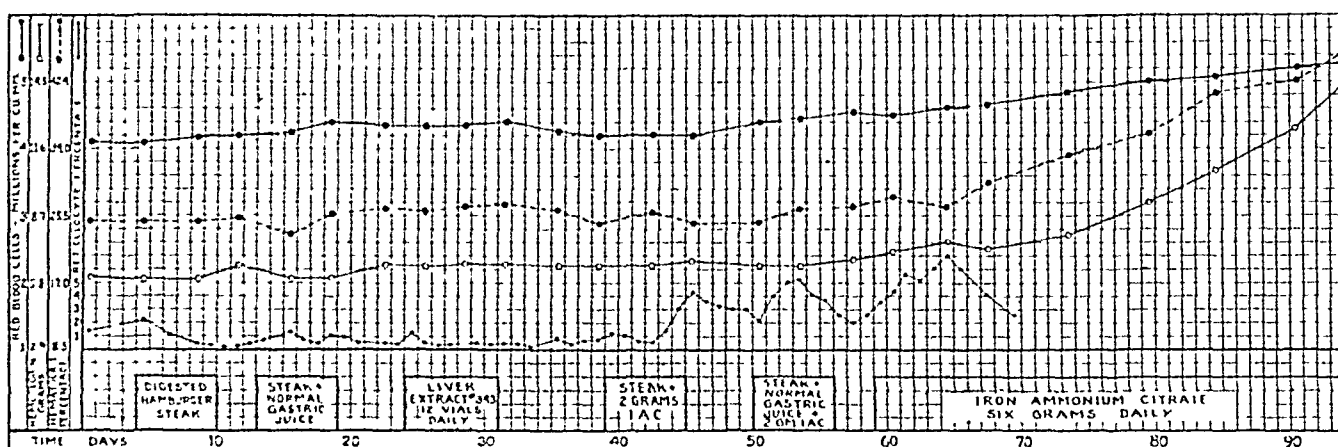


Chart 1 (case 1).—The ineffectiveness of beef steak digested with normal gastric juice and of large amounts of liver extract in securing remission of the anemia. Response of the reticulocytes followed the administration of 2 Gm. of iron ammonium citrate with steak digested with hydrochloric acid and pepsin, and also following the administration of 2 Gm. of iron ammonium citrate with steak digested with normal gastric juice. A third response of the reticulocytes accompanied by a rapid increase in the hemoglobin and hematocrit percentage followed when 6 Gm. of iron ammonium citrate was given daily.

#### REPORT OF CASES

CASE 1.—O. B. was given daily for six days 200 Gm. of beef steak digested with pepsin and hydrochloric acid. No change in the blood counts occurred. She was then given six daily feedings of 200 Gm. of beef steak digested with 100 cc. of normal gastric juice; there was still no change in the blood. She next received 12 vials of liver extract daily for six days, again without evidence of improvement in the blood or in the general condition. The next procedure was the administration of six daily doses of 2 Gm. of iron ammonium citrate and 200 Gm.

of beef steak which had been digested with hydrochloric acid and pepsin. A prompt rise of the reticulocytes to 4.2 per cent followed. Two grams of iron ammonium citrate was then fed daily with 200 Gm. of beef steak digested in 100 cc. of normal gastric juice; the reticulocytes rose to 5.1 per cent. Finally, daily doses of 6 Gm. of iron ammonium citrate were given alone. A third rise of the reticulocytes to 7 per cent followed, with an increase in the hemoglobin and in the volume of packed red blood cells. An improvement in the patient's general condition also occurred.

The bleeding and clotting times were normal.

TABLE 2 (CASE 2).—*Results of the Examination of the Blood*

	On Admission	On Discharge
Red blood count.....	3,970,000	4,640,000
Hemoglobin .....	6.3 Gm. (42%)	14.1 Gm. (97%)
Volume of packed red cells.....	25.2 per cent	39.9 per cent
Mean corpuscular volume.....	64 cubic microns	86 cubic microns
Mean corpuscular hemoglobin.....	16 micromicrograms	30 micromicrograms
Mean corpuscular hemoglobin concentration.....	25 per cent	35 per cent
Reticulocytes .....	0.4 per cent	
White blood count.....	4,150	
Platelets .....	216,000	
Icteric index .....	5	

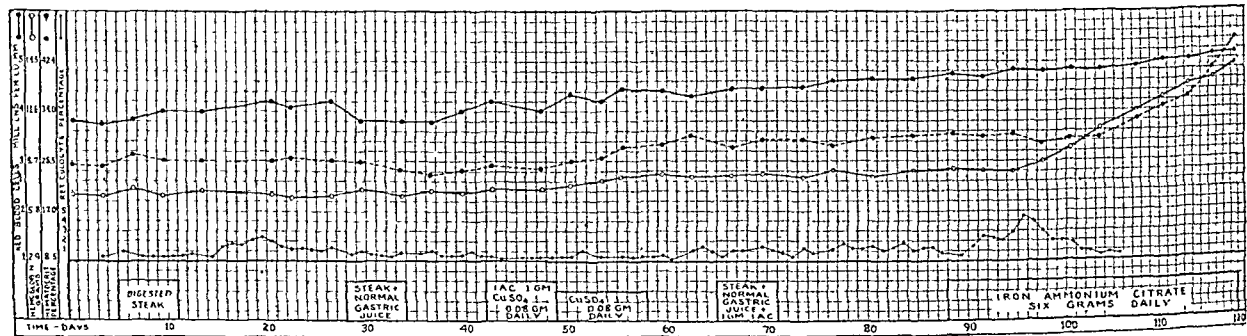


Chart 2 (case 2).—No response of the reticulocytes or improvement in the blood occurred when the following feedings were administered: steak digested with normal gastric juice; 1 Gm. of iron ammonium citrate with 0.08 Gm. of copper sulphate; 0.08 Gm. of copper sulphate given alone; 1 Gm. of iron ammonium citrate given with steak digested with normal gastric juice. Prompt response of the reticulocyte, hemoglobin and hematocrit percentages followed the daily administration of 6 Gm. of iron ammonium citrate.

The blood smear on admission showed a preponderance of small, pale red cells with central achromia and slight poikilocytosis. The white cells and platelets were normal. No abnormalities were noticeable in the blood smears on discharge.

CASE 2.—As in the preceding case, 200 Gm. of beef steak digested with hydrochloric acid and pepsin was administered daily for six days to the patient A. T. This was followed by six daily feedings of 200 Gm. of beef steak digested with 100 cc. of normal gastric juice. In neither instance was there a significant increase in the percentage of reticulocytes. The patient was next given 1 Gm. of iron ammonium citrate with 0.08 Gm. of copper sulphate daily for six days,

the administration of the latter being continued for nine days after the iron was discontinued. Subsequently, 1 Gm. of iron ammonium citrate was given in 200 Gm. of beef steak and 100 cc. of normal gastric juice. These modes of treatment were likewise ineffectual. Finally iron ammonium citrate was given alone in doses of 6 Gm. daily. A prompt rise of the reticulocytes, a rapid return of the red blood cell count, the hemoglobin and the volume of packed red cells to normal and a gradual disappearance of the patient's symptoms followed.

The blood smear examined on admission revealed that the majority of the red cells were small and pale; there were a number of elliptic erythrocytes, and 1

TABLE 3 (CASE 3).—*Results of the Examination of the Blood*

	On Admission	On Discharge
Red blood count.....	4,320,000	5,100,000
Hemoglobin .....	7.2 Gm. (50%)	12.2 Gm. (84%)
Volume of packed red cells.....	27 per cent	38.2 per cent
Mean corpuscular volume.....	63 cubic microns	75 cubic microns
Mean corpuscular hemoglobin.....	17 micromicrograms	24 micromicrograms
Mean corpuscular hemoglobin concentration.....	27 per cent	32 per cent
Reticulocytes .....	0.2 per cent	
White blood count.....	8,000	
Icteric index .....	5	

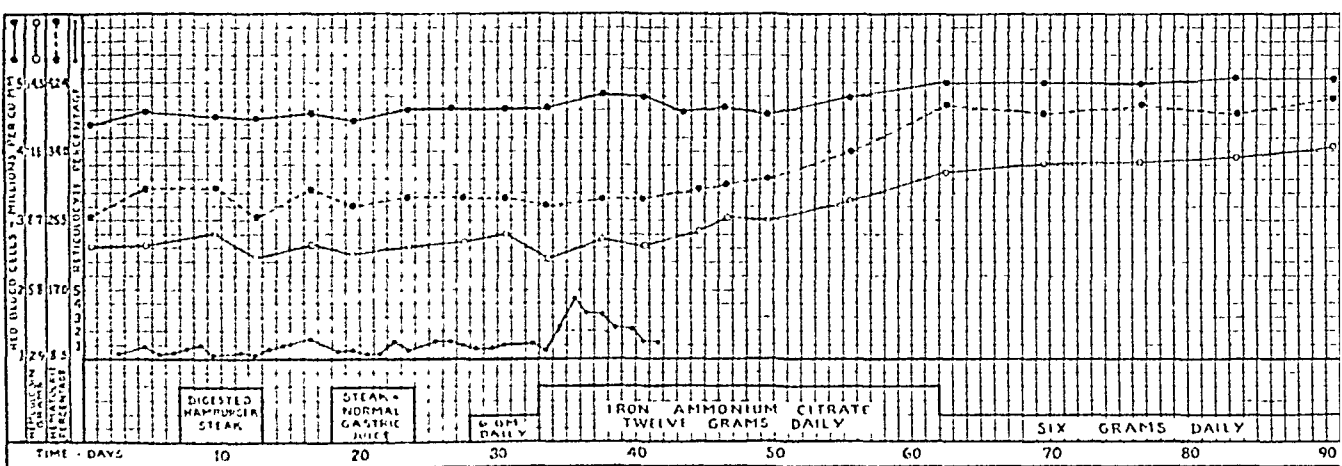


Chart 3 (case 3).—No response of the reticulocytes followed the administration of beef steak digested with normal gastric juice. The increase in the reticulocytes, the hemoglobin and the volume of packed red cells followed treatment with iron.

normoblast per one hundred leukocytes was found. No abnormal white cells were observed. On discharge, the stained films showed no abnormalities.

CASE 3.—R. M. was given six daily feedings of 200 Gm. of beef steak digested with pepsin and hydrochloric acid. No response of the reticulocytes occurred. This was followed by six daily feedings of steak digested with 100 cc. of normal gastric juice; again there was no influence on the number of reticulocytes. Only when iron ammonium citrate was given in doses of 6 Gm. daily did a small response of the reticulocytes (3.8 per cent) and a slow increase in the hematocrit percentage and red blood cell count occur. The changes in the blood became somewhat more rapid when 12 Gm. of iron ammonium citrate was given daily.



In the blood smear on admission, cells of all sizes from large, well filled macrocytes to the smallest, pale microcytes, were found. The latter predominated in number. Many elliptic cells were present. There were no sickle cells in the fresh blood. There was a slight shift to the left in the myeloid leukocytes. The blood smear on discharge did not show these abnormalities.

CASE 4.—M. R. was given six daily feedings of 200 Gm. of beef steak digested with 100 cc. of normal gastric juice. No rise of reticulocytes or change

TABLE 4 (CASE 4).—*Results of the Examination of the Blood*

	On Admission	On Discharge
Red blood count.....	5,400,000	5,100,000
Hemoglobin .....	8.5 Gm. (55%)	12.6 Gm. (87%)
Volume of packed red cells.....	30.6 per cent	40.4 per cent
Mean corpuscular volume.....	52 cubic microns	78 cubic microns
Mean corpuscular hemoglobin.....	14 micromicrograms	24 micromicrograms
Mean corpuscular hemoglobin concentration.....	28 per cent	31 per cent
Reticulocytes .....	0.2 per cent	
White blood count.....	4,500	
Icteric index .....	5	

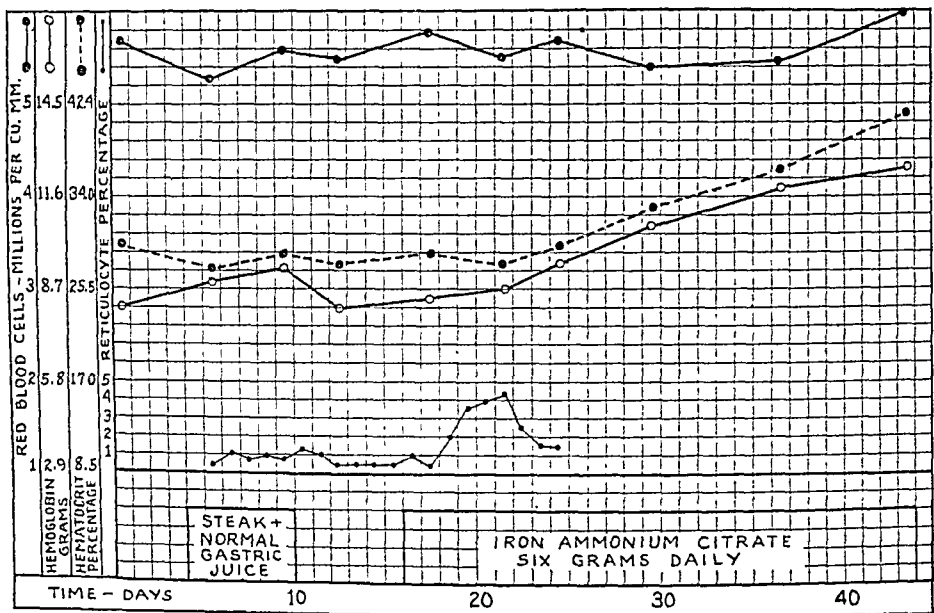


Chart 4 (case 4).—The reticulocytes failed to respond to feedings of beef steak digested with normal gastric juice. A rapid increase in the reticulocytes, the hemoglobin and the volume of packed red cells followed the administration of iron.

in the red blood count or in the hemoglobin content followed this procedure. Four days after administration of iron ammonium citrate, 6 Gm. daily, was started, a definite response of the reticulocytes occurred, and this was followed by a rapid rise in the hemoglobin and in the volume of packed red cells to almost normal readings. These changes were accompanied by symptomatic improvement.

A blood smear taken on admission showed that the majority of the red blood cells were small and pale. There were no abnormalities in the white cells, and the platelets were normal.

CASE 5.—R. A. was given 200 Gm. of beef steak digested with 100 cc. of normal gastric juice daily for six days. There was no evidence of a response of the reticulocytes. Following the administration of 6 Gm. of iron ammonium citrate daily, there was a prompt response of the reticulocytes, the hemoglobin and the volume of packed red cells.

Blood smears examined on admission showed that the red blood cells were small and pale, with marked central achromia, and that the white cells were normal.

TABLE 5 (CASE 5).—Results of the Examination of the Blood

	On Admission	On Discharge
Red blood count.....	4,860,000	4,570,000
Hemoglobin .....	7.3 Gm. (50%)	14 Gm. (97%)
Volume of packed red cells.....	28.9 per cent	40.1 per cent
Mean corpuscular volume.....	59 cubic microns	88 cubic microns
Mean corpuscular hemoglobin.....	15 micromicrograms	31 micromicrograms
Mean corpuscular hemoglobin concentration.....	25 per cent	35 per cent
White blood count.....	5,000	
Icteric index .....	3	

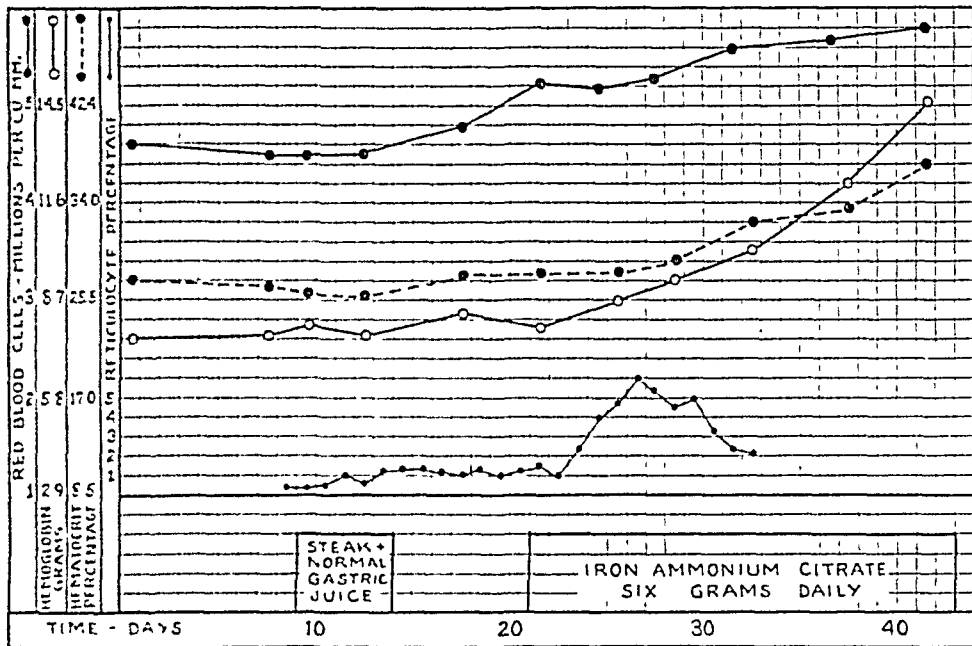


Chart 5 (case 5).—Administration of steak digested with normal gastric juice was ineffective as compared with iron therapy in obtaining prompt remission of anemia.

#### COMMENT

From these experiments it seems clear that in idiopathic hypochromic anemia the feeding of mixtures of beef steak and normal gastric juice is without effect on the blood. It appears that in this form of anemia there is not lacking a specific substance of the sort that is absent in pernicious anemia. This is an important point of difference between the two anemias, which, because of the many symptoms and physical

findings common to both and because of the occurrence of achlorhydria in both, have frequently been compared. .

From the two experiments recorded, it is not possible to draw any conclusions concerning the influence of the normal gastric secretion on the absorption of inorganic iron. Further studies along these lines are in progress. It is of significance, however, that in the presence of the gastric deficiency which hypothetically permitted anemia to develop, the anemia was relieved by administration of large amounts of iron.

#### SUMMARY

Five patients with idiopathic hypochromic anemia were treated with beef steak digested with normal gastric juice, according to the method used by Castle in causing a remission in pernicious anemia. In no instance was there an increase in the percentage of reticulocytes or a rise of the hemoglobin, the volume of packed red cells or the red blood count.

Following the administration in each instance of suitable amounts of iron ammonium citrate, the percentage of the reticulocytes rose promptly, and there soon followed a rapid increase of hemoglobin, an increase in the volume of packed red blood cells and improvement in the patients' symptoms and general appearance.

# CINCHOPHEN TOXICOSIS

## RESULTS OF EXPERIMENTAL SUBACUTE AND CHRONIC CINCHOPHEN POISONING

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AND

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Recent clinical reports on cinchophen toxicosis leave the impression that injury to the liver is an established and characteristic phenomenon of the drug's action. Unfortunately, however, much of the writing on this phenomenon is distinguished by the *post hoc ergo propter hoc* type of reasoning. While such reasoning errs on the side of safety in medication, it has little or no weight as scientific evidence. Conjectural and deductive reasoning cannot take the place of the controlled experiment. The injury to the liver should be experimentally reproducible if the effect is to be ascribed to a direct action of cinchophen. That is, a direct relationship of cause and effect should be demonstrated. But this has not been achieved, even with doses of the drug which would be therapeutically undesirable or prohibitive, as this paper will show. However, deleterious effects on young growing animals on a dietary containing large amounts of the drug are demonstrable.

In our work with animals, it was aimed to comply with conditions which appear to determine clinical cinchophen toxicosis. Essentially, these conditions were: continued medication with tolerated doses which would virtually keep up a steady poisoning of the body during long periods, and preexisting hepatic disease or injury which might make the liver hypersusceptible to cinchophen. In the feeding experiments with young animals, the effects on growth and on body weight indicated general effects which might be due to unpalatability of the medicated food, to disturbed appetite or to specific injury of organs or tissues. In the absence of demonstrable changes in the liver in the feeding experiments, the drug was injected intramuscularly, which guaranteed systemic absorption and action. Prior experimental injury of the liver was effected with chloroform and phosphorus. Combined with the general procedures, there were specific tests to demonstrate hepatic injury, such as that for bile in the urine and that for deranged capacity for the excretion of dye. The livers of all the animals were removed and submitted to independent histologic study by competent pathologists,

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namely, Prof. William Ophüls and Dr. David Wood of the department of pathology of Stanford University.

A discussion of the clinical literature has been omitted because there have been so many clinical papers written on this form of toxicosis, and each paper has recapitulated all the preceding ones; another recapitulation would be a work of supererogation. Among the latest and the best of these papers are those by Weis,<sup>1</sup> who has given a tabular summary of the essential data in all the previous clinical papers, and by Reah,<sup>2</sup> who summarized experiences in England and gave important hints. Dr. John V. Barrow of Los Angeles has fairly and conservatively stated the case for and against cinchophen toxicosis in a discussion of the recent paper by Parsons and Harding.<sup>3</sup> In a word, the outstanding feature of the extensive recitation of the clinical histories of cases of this poisoning is the lesson on the dangers of self-medication. Commonly, the drug has been taken by a patient for some symptom or supposed disease, and occasionally it has been carelessly prescribed by a physician. Generally, large doses have been taken or given regularly for long periods and a total of 100 Gm. or so has been taken before deleterious effects have been recognized. Then an illness has occurred with dramatic suddenness, the outcome frequently being fatal and the liver being found markedly degenerated. Occasionally, severe effects and even death have been attributed to small doses. More important is the association with cinchophen toxicosis of such conditions as chronic arthritis, nephritis, alcoholism, protein shock, syphilis, carcinoma, disease of the gallbladder and pregnancy. Any one of these conditions, however, might be sufficient in itself to injure or to destroy the liver. There are other manifestations of cinchophen poisoning, such as the cutaneous, vasomotor and gastro-intestinal, which appear to be more prominent than the hepatic, and probably more constant, but they, too, are not peculiar to cinchophen.

We have no desire to prejudice or to weaken the case against the evils of self-medication, or to make light of possible deleterious consequences of legitimate medication with this drug. However, before the clinical results thus far reported are scientifically acceptable, there must be more convincing evidence of a direct relationship between the cause and the effect, which so far has failed to be established by experimentation. The experimental results which we have obtained may be presented best under the general headings of chronic and subacute poisoning, according to the time elements involved.

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1. Weis, C. R.: Toxic Cirrhosis of Liver Due to Cinchophen Compounds: Report of Three Fatal Cases, *J. A. M. A.* **99**:21 (July 2) 1932.

2. Reah: *Lancet* **2**:504, 1932.

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## CHRONIC POISONING

Young white rats were given a whole synthetic diet<sup>4</sup> containing 0.5, 1 and 2.5 per cent concentrations of cinchophen and 1 and 2.5 per cent concentrations of neocinchophen. The feeding was begun with rats weighing about 50 Gm. and was kept up for twenty weeks with the majority of the groups. Five rats of the same sex were used in a group. Free access to the diet and to water was allowed. The rats

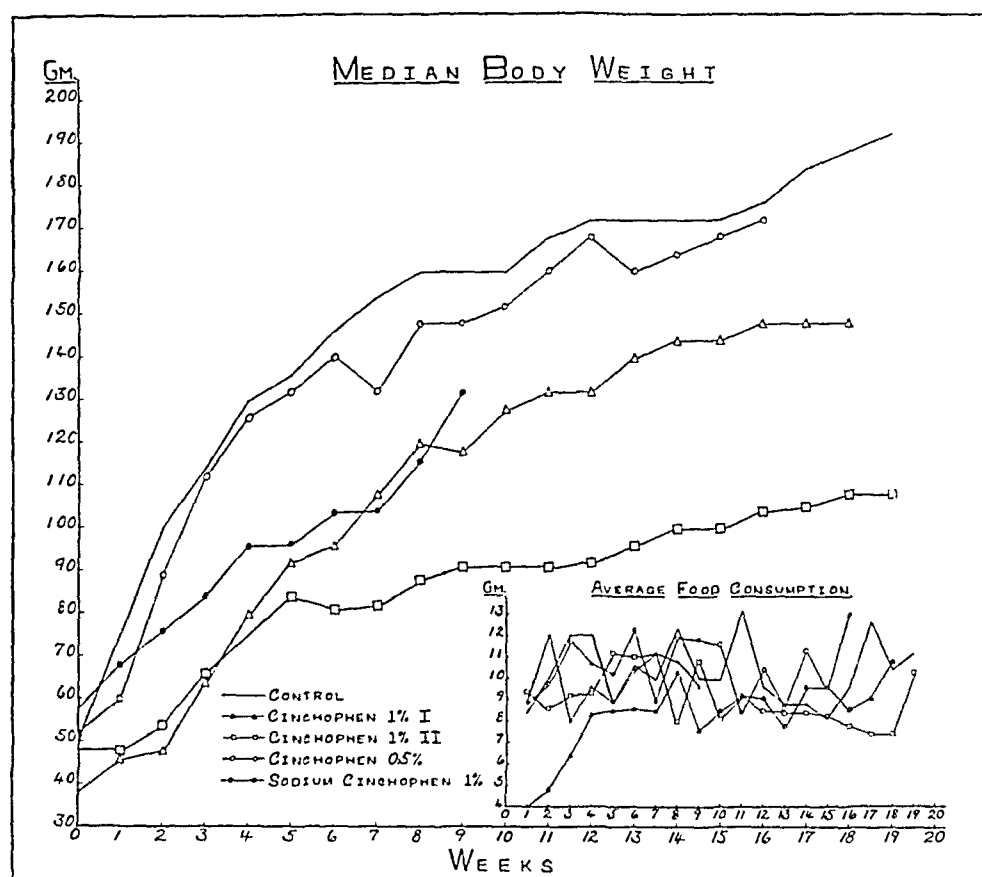


Chart 1.—Continued administration of cinchophen to white rats: changes in body weight and in consumption of food.

were weighed weekly, and the food as often as necessary. Two groups of rats kept on a diet of unmedicated food acted as controls. Careful notes were made on general behavior and on symptoms. The average weekly changes in body weight, growth and consumption of food of all the rats, except those receiving 2.5 per cent cinchophen, are shown in charts 1 and 2. Other data are summarized in table 1.

4. The composition of the diet was: feed cornmeal, 68 per cent; linseed oil cake meal, 10 per cent; dried ground alfalfa, 2 per cent; powdered casein, 10 per cent; lard, 5 per cent; cod liver oil, 3 per cent; bone ash, 1.5 per cent, and sodium chloride, 0.5 per cent.

TABLE 1.—*Chronic Poisoning with Cinchophen and Neocinchophen in Rats: Food Consumption, Changes in Body Weight, Dosage of Cinchophen*

Drug, per Cent in Food	Daily Food Consumption		Duration of Feeding Experiment	Loss of Body Weight, per Cent		Daily Intake of Cinchophen, Gm. per Kilogram of Weight of Rat		Estimated Total Intake of Cinchophen for a Man Weighing 70 Kg.	Estimated Intake of Cinchophen for a Man Weighing 70 Kg.	
	Range	Median	Weeks	Range*	Median	Range	Median	Intake of Cinchophen, Gm. per Kg. of Weight of Rat, Median	Equivalence of Life Span in Years	Total Intestion During Period of Years
Unmedicated controls.....	8.1-13.1	10.0	19	.....	.....	.....	.....	.....	.....	.....
Cinchophen, 0.5%.....	8.4-13	10.5	16	1.7-20.0	4.4	0.26-0.73	0.380	42.6	6	58.3 128.3
Cinchophen (I), 1%.....	4 -10.3	8.6	18	15.9-52.0	28.6	0.553-1.037	0.707	89.1	6½	120.5 265.1
Cinchophen (II), 1%.....	7.4-11.2	8.9	19	36.0-46.7	43.1	0.685-1.958	0.953	126.8	6½	162.4 357.3
Sodium cinchophen, 1%†.....	8 -12	9.6	9	9.3-32.4	26.3	0.72-1.572	0.908	62.9	3½	69.9 89.3 196.5
Neocinchophen, 1%.....	8 -11.3	9.3	16	5.6-23.0	15.7	0.554-1.372	0.693	77.6	6	48.5 106.2 233.6
Neocinchophen, 2.5%.....	7.2-11.6	9.8	9	14.6-52.9	36.9	2.034-4.263	2.808	176.9	3½	196.6 251.3 552.9 (about 16½ bushels)

\* Generally the highest intake occurred in the beginning and the lowest toward the close of the experiment.

† The cinchophen content of 1 per cent sodium cinchophen is 1.08 per cent.

*Cinchophen* (chart 1 and table 1).—The rats which received 2.5 per cent cinchophen died in from five to twenty days. Probably this was the result of starvation, as the animals refused to eat this food; hence, the results were discarded. Food containing the lower concentrations of the drug was readily eaten and caused definite loss of body weight and stunting of growth. The effects were demonstrable one week after feeding, and were seemingly present even with the lowest concentration used, namely, 0.5 per cent. Retardation of growth was definite at the end of one and two months. At the end of five months, the rats on 1 per cent cinchophen in group II were approximately one-half the size, and in group I, two-thirds the size, of the controls. The median loss of body weight for rats in group II was 28.6 per cent, and for those in group I, 43.1 per cent. One per cent sodium cinchophen, which is the more soluble form of the drug, was given for nine weeks, or for about one-half the time of the acid form of the drug, and the effects were the same, the median loss of body weight being 26.3 per cent.

The decreased body weight and the retarded growth could not have been due entirely to decreased food consumption, although some of the rats given cinchophen tended to eat less. For instance, the rats on 0.5 per cent cinchophen ate a median of 10.5 Gm. (range 8.1 to 13.1 Gm.), and the controls, 10 Gm. (range 8.4 to 13.1 Gm.) daily. Yet the loss of body weight in these cinchophenized rats was definite though comparatively less than in the rats on 1 per cent cinchophen. The latter in group I ate a median of 8.6 Gm. (range 4 to 10.3 Gm.) daily. Again, the median daily consumption of food of rats given 1 per cent sodium cinchophen was 9.6 Gm. (range 8 to 12 Gm.), which was similar to that of the controls, but the loss of body weight was the same as in rats of group I, namely, 28.6 per cent. Finally, the comparatively small decreases in the consumption of food of rats in groups I and II, namely, 14 and 11 per cent, respectively (compared with the intake of the controls), could not satisfactorily explain the comparatively greater losses of 28.6 and 43.1 per cent in their body weights. Hence, it is believed that, in the rats receiving cinchophen, there was lacking a correlation between changes in body weight and consumption of food, and therefore the loss of body weight is to be attributed principally to the effects of the cinchophen and not to lack of food.

Aside from the losses in body weight and the stunting of growth, there were no definite manifestations of poisoning among the rats receiving cinchophen. In general, however, the rats receiving the drug were not as lively as the controls. One of the fifteen rats receiving cinchophen died, and another showed hematuria, but these phenomena were probably accidental. The urine of all cinchophenized rats was



from orange-red to red, owing to the presence of the drug or its products, which was confirmed by Scheunemann's test.<sup>5</sup> This result indicated definite gastro-intestinal absorption of the drug. The urine of control untreated rats failed to react to this test. The van den Bergh tests for bile pigment and salts in the urine of cinchophenized rats were uniformly negative, as was also the heat-acetic acid test for albumin. The livers of all cinchophenized rats, obtained immediately

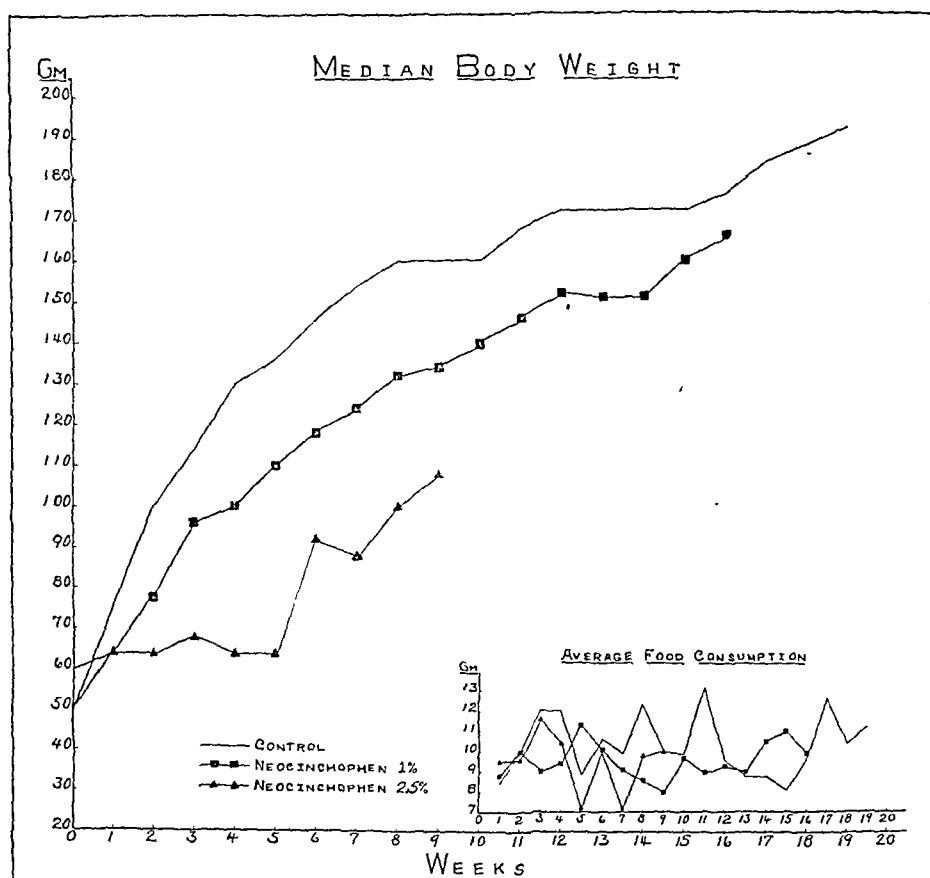


Chart 2.—Continued administration of neocinchophen to white rats: changes in body weight and in consumption of food.

after the rats were killed at the end of the experiments, appeared grossly and microscopically (frozen and paraffin sections) like those of the control rats. According to the pathologists who examined the hepatic tissues, there were no evidences of pathologic changes. Therefore, the retarded growth and the loss of body weight of the rats that received cinchophen could not be attributed to injury or to derangement of the liver, whatever else might have been the mechanism of the action of the drug.

5. Scheunemann: Arch. f. exper. Path. u. Pharmakol. 100:51, 1923.

*Neocinchophen* (chart 2 and table 1).—The therapeutic use of this ester in place of cinchophen has been advised in view of the reported injurious effects of the latter. However, in our feeding experiments with rats, the effects on body weight and on growth were the same as those of cinchophen. The loss of body weight and the stunting of growth were greater with the higher concentration, namely 2.5 per cent, than with the lower concentration of 1 per cent. The median loss of body weight during sixteen weeks of feeding of the 1 per cent concentration was 15.7 per cent (range 5.6 to 23 per cent), and during nine weeks of feeding of the 2.5 per cent concentration, 36.9 per cent (range 14.6 to 52.9 per cent). These changes could have been due only partly to diminished consumption of food, since both groups of rats ate little less than the controls. Those given the 1 per cent concentration ate a median of 9.3 Gm. (range 8 to 11.3 Gm.) daily, and those on the 2.5 per cent concentration, 9.8 Gm. (range 7.2 to 11.6 Gm.), or about from 2 to 7 per cent less than the controls, which ate a median of 10 Gm. daily. The weekly fluctuations in the consumption of food were somewhat less for the rats on 1 per cent neocinchophen than for those on the 2.5 per cent concentration and on the control unmedicated food. The comparatively small reduction in consumption of food was not surprising as far as palatability is concerned, since the ester is practically tasteless, owing to its low solubility. The comparatively greater reduction in body weight may therefore be attributed to some systemic action of the neocinchophen, as was the case with cinchophen. This is supported by the fact that decreases in body weight and in growth were greater with the higher concentration of neocinchophen used.

Only one of the five rats receiving 1 per cent neocinchophen died before the end of the experiment. In all other respects, such as general symptoms, biliuria, albuminuria and changes in the liver, the neocinchophenized rats showed nothing abnormal, just as was true of the cinchophenized rats. Chemical tests for the presence of the drug and its products in the urine were positive, as with cinchophen; absorption, therefore, was definitely established. From these results, it would appear that the stunting of growth was not mediated through some specific organ or function, but rather was general, as was the case with cinchophen.

*Dosage of the Cinchophens and Its Significance* (table 1).—It is interesting and important to correlate the doses of cinchophen and neocinchophen used in the feeding experiments for the production of chronic poisoning just described with a number of factors in order to appreciate the possible significance of the results obtained. We shall consider cinchophen first. The median daily intake per kilogram of weight ranged from 0.38 to 0.998 Gm. for from one-seventeenth to

one-ninth the span of life. The total amounts of cinchophen ingested per kilogram of weight during these periods were from 42.6 to 126.8 Gm. (medians). These are enormous doses when translated into quantities for a man weighing 70 Kg. with a span of life of 60 years. According to the estimates made, the equivalents for such a man would be about as follows: the eating of poisoned (cinchophenized) food for from three and one-half to six and two-thirds years; the ingestion of total daily quantities of the drug of from 26.6 to 69.9 Gm., and the taking of a total quantity of the drug during the periods estimated of from 58.3 Kg., or 128.3 pounds, to 162.4 Kg., or 357.3 pounds. If one assumes that the effects in rats and in men are similar, there might be some decrease in body weight, or in young persons a stunting of growth, which would be serious, but so far as deleterious effects on the liver are concerned, these would be negligible or nonexistent. But it is scarcely conceivable that such enormous quantities of the drug could be taken for such long periods as was the case in the feeding of rats. Even more important is the fact that the ingestion of such quantities has not been recorded in any of the clinical reports of cinchophen poisoning. In contrast with all these large estimated quantities are the therapeutic doses, which range from about 0.01 to 0.03 Gm. to from 0.15 to 0.3 Gm. per kilogram daily, commonly given in the intensive treatment of rheumatic fever during the course of a day or for a number of days. It is doses of this size that are mentioned in the clinical reports, generally for much shorter periods than could be tolerated according to our estimates. The significance of all this is that the toxicosis of clinical patients is concerned with, or conditioned by, something other than cinchophen. At least, the dosage of cinchophen which may be taken by a patient is not a criterion of the possible outcome, nor is even the period of medication or the clinical condition as a whole or that of the liver.

What has been said regarding the human equivalents of factors with cinchophen applies equally to neocinchophen, except that the ester could be given more liberally. For instance, for a 15.7 per cent loss of body weight, a man weighing 70 Kg. might have to take 48.5 Gm. of neocinchophen for six years, or a total of about 106.2 Kg. or 233.6 pounds, of the drug. For a 36.9 per cent loss, occurring during three and one-half years of steady medication, the same man would take about 196.6 Gm. daily, or a total of 251.3 Kg., or 552.9 pounds (about 16½ bushels). These enormous quantities, practically impossible of administration in practice, whether by self-medication or by careless prescribing, merely emphasize the great resistance of healthy livers to this drug. One possibility always remains, and that is incomplete absorption, which could more easily occur with neocinchophen than with cinchophen, so

that such large quantities as are indicated by our equivalents would not be wholly effective. Nevertheless, such equivalents were ingested with food by the rats, as they might be by man, and, what is equally important, the positive chemical tests showed that the drug was absorbed under these conditions. This brings us to the subacute experiments on healthy and previously poisoned rabbits and on one animal given cinchophen intramuscularly, which assured systemic absorption and action. The livers of all these rabbits were tested for functional efficiency by means of a dye, and the majority were examined histologically by the same pathologists who examined the rats' livers.

#### SUBACUTE POISONING

Eighteen rabbits were used. The rose bengal test of liver function, described by Delprat,<sup>6</sup> was applied, 3 mg. of the dye per kilogram of body weight being given intravenously and samples of plasma (cardiac blood) being collected two, five, fifteen, thirty and sixty minutes after injection. The general plan of the experiment follows: First the dye test was applied; the rabbit was allowed to recover for one day; then the cinchophen was administered gastrically by means of a suitable catheter and bulb three times weekly for periods of from one week to thirteen weeks, and the dye test was repeated at intervals during the course of medication with cinchophen. Generally a dye test was made after one week of medication, and then after varying periods of from two to about seven weeks. Intramuscular injection of cinchophen, dissolved in water with the aid of sodium hydroxide, was made in one rabbit, which showed some uneasiness after the injection. As the changes differed in no essential respects from those produced by gastric administration, and as parenteral administrations in rats had already been tried on a large scale by Riechle,<sup>7</sup> we did not continue to use intramuscular injections. After all, there were more important aspects of gastric medication for investigation. The rabbits poisoned with chloroform and with phosphorus received the dye test before and after the administration of the poisons as well as after cinchophen medication; the details of these experiments will be given later. The plan of the experiments necessitated repeated cardiac punctures which resulted in a number of accidental deaths, but only the data for rabbits on which the experiments were successfully carried through are reported. A summary of essential data on medication and of results on functional and morphologic changes in the liver in all the rabbits are given in table 2. The data from the dye tests are presented in chart 3.

6. Delprat, G. D.: Studies of Liver Function: Rose Bengal Elimination from the Blood as Influenced by Liver Injury, *Arch. Int. Med.* **32**:401 (Sept.) 1923.

7. Reichle, Herbert S.: Cinchophen Poisoning: An Attempt to Produce Toxic Cirrhosis of the Liver in Rats, *Arch. Int. Med.* **49**:215 (Feb.) 1932.

TABLE 2.—*Dosage and Hepatic Effects of Cinchophen Administered Orally in Healthy Rabbits and in Those Previously Poisoned with Chloroform and Phosphorus*

Rabbit	Total Dose of Cinchophen, Gm. per Kg.	Period of Medication, Days	Equivalent Period of Human Life	Hepatic Changes	
				Functional Efficiency†	Morphology
Cinchophen					
1	0.3	7	8 wks.	Unchanged from control	
2	0.3	7	8 wks.	Unchanged from control	
3	0.6	7	8 wks.	Unchanged from control	
4	0.6 1.0	7 14	8 wks. 16 wks.	Decrease Marked decrease	
5	0.6* 2.4*	7 50	8 wks. 1½ yrs.	Unchanged from control Unchanged from control Unchanged after five weeks of rest	Slight nuclear damage; focal necrosis and hydropic degeneration
6	0.6 1.2 1.8 5.2	7 11 23 89	8 wks. 4 mos. 6 mos. 2 yrs.	Unchanged from control Unchanged from control Unchanged from control Unchanged from control	Focal necrosis; hydropic degeneration; some nuclear damage
Chloroform‡ and Cinchophen					
7	0.6	7	8 wks.	Same as after chloroform	
8	0.6	7	8 wks.	Approaching control	Normal
9	0.6	7	8 wks.	Approaching control	Slight to moderate cloudy swelling; questionable beginning hepatic degeneration
10	0.6 2.4	7 45	8 wks. 1 yr.	Unchanged from chloroform Tendency to some decrease	Focal necrosis; hydropic degeneration; nuclear damage
11	0.6 2.4	7 44	8 wks. 1 yr.	Same as after chloroform Greater decrease than after chloroform	Cells swollen; glycogen infiltration; karyolysis; questionable beginning hepatic degeneration
12	0.6 2.8	7 52	8 wks. 1½ yrs.	Approaching control Unchanged from control	Slight cloudy swelling
Phosphorus§ and Cinchophen					
13	0.6	7	8 wks.	Approaching control	Slight to moderate cloudy swelling
14	0.6	7	8 wks.	Approaching control	Slight to moderate cloudy swelling
15	0.6	7	8 wks.	Approaching control	Moderate cloudy swelling and congestion
16	0.6 1.6	8 28	8 wks. 8 mos.	Approaching control Approaching control	Slight cloudy swelling
17	None	None	.....	.....	Marked periportal necrosis; cloudy swelling and vacuolization of liver cells; fatty and hydropic degeneration
18	None	None	.....	.....	Moderate cloudy swelling and detachment of central cells; definite hepatic degeneration

\* Intramuscular injections.

† Results of dye tests in chart 1.

‡ Preliminary fifteen minute daily inhalations for one week.

§ Preliminary injections of phosphorus in olive oil for one week; total dose of phosphorus, 6 mg. per kilogram of body weight.

*Cinchophen* (table 2 and chart 3).—It is seen that the total doses of cinchophen administered during the first week to each of six rabbits ranged from 0.3 to 0.6 Gm. per kilogram of body weight, or the equivalent of from 21 to 42 Gm. for a man weighing 70 Kg. during a period of eight weeks. The life expectancy of a rabbit is about eight years, so that one week of a rabbit's life is equal to about eight weeks of a man's life (expectancy sixty years), and one year of a rabbit's life is equal to eight years of a man's life. Only rabbit 4, which

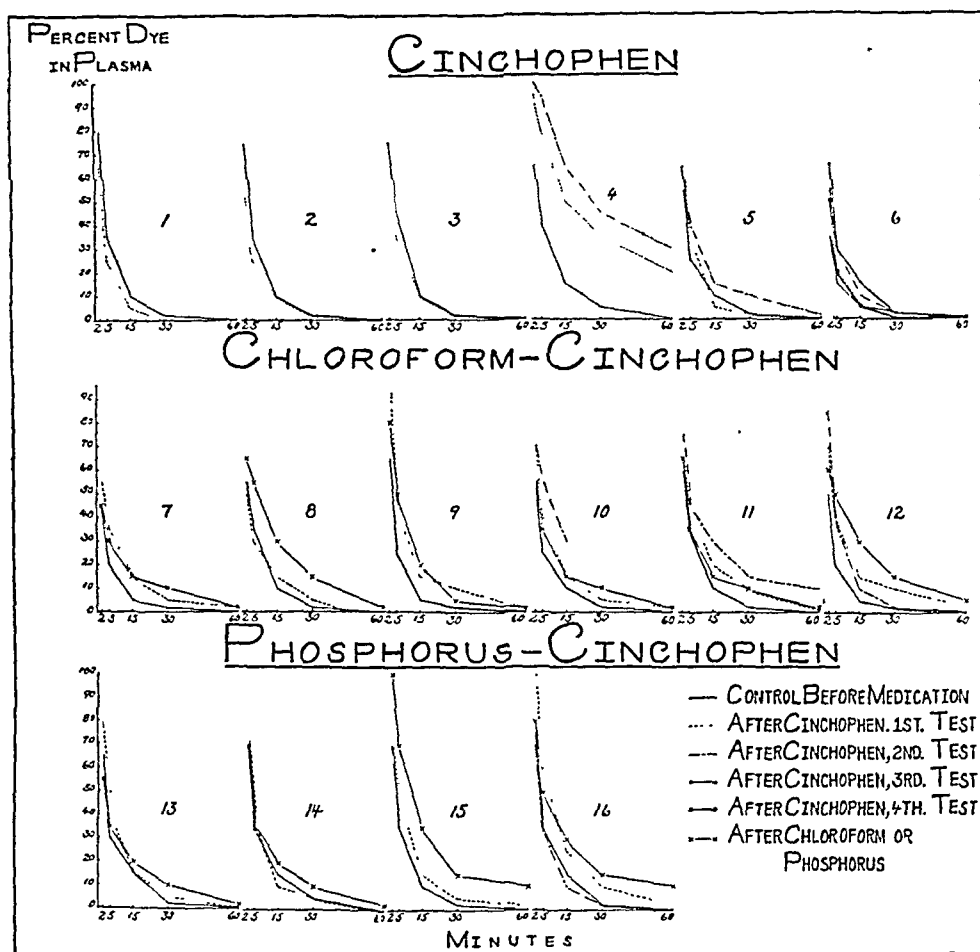


Chart 3.—Results of liver function tests in rabbits receiving cinchophen, chloroform and cinchophen, and phosphorus and cinchophen. The curves show the percentage of rose bengal in the plasma in rabbits 1 to 16.

received 0.6 Gm. of cinchophen per kilogram, showed a decrease in hepatic functional efficiency. Continuation of the medication for two, three, seven and thirteen weeks in rabbits 4, 5 and 6, with total doses of from 1 to 5.2 Gm. per kilogram, caused no change in the functional efficiency of the liver in two of the three animals. After two weeks of medication, rabbit 4 showed a marked decrease, i. e., prolonged retention of the dye, while rabbits 5 and 6, which received the highest doses, showed no impairment of capacity for excretion of dye. How-

ever, the livers of rabbits 5 and 6 showed pathologic changes, namely, focal necrosis and hydropic degeneration after total doses of 2.4 and 5.2 Gm. per kilogram, respectively. These morphologic changes in the liver were interpreted by Drs. Ophüls and Wood as mild, scattered injuries. However, when these changes are compared with the generally less severe or negligible, though variable, changes in the livers of rabbits which received chloroform and phosphorus in addition to similar doses of cinchophen, to be discussed presently, the precise significance of these mild hepatic injuries from cinchophen alone is not easily or clearly determinable. It is to be noted that rabbit 5 received the drug intramuscularly, but rabbit 6, which received it gastrically, showed the same changes. Unfortunately, histologic study of the livers of the remaining rabbits was not made. Tests for bile in urine were not made, but the appearance of the urine was not unusual or abnormal.

The equivalents in total dosage and period of medication for a man weighing 70 Kg., according to the same factors in the extended medication of these rabbits, were estimated about as follows: From 70 to 364 Gm., or from  $2\frac{1}{2}$  to  $11\frac{1}{3}$  ounces, of cinchophen might be taken during periods of from sixteen weeks to one and one-third and two years. Such continued medication might occur under clinical conditions, and, if so, most likely for a short period, such as sixteen weeks, which has been reported. The highest dosage would correspond to the taking of about 7.5 grains (0.5 Gm.) daily for two years without functional impairment of the liver, but possibly with some mild scattered morphologic injuries. But about 9 grains (0.54 Gm.), or practically two 5 grain tablets, could be taken each day for four months, presumably without injury to the liver.

*Chloroform and Cinchophen* (table 2 and chart 3).—Daily inhalations of chloroform to produce complete anesthesia (complete relaxation and abolition of reflexes) for fifteen minutes during seven consecutive days were given to six rabbits before the cinchophen was administered. Moderate though definite impairment of hepatic functional efficiency resulted in every anesthetized rabbit, as might have been expected. There were increases of about from 5 to 20 per cent, occasionally 30 per cent, in the dye content of the blood, and delays of about ten minutes in complete removal. Then followed medication with cinchophen in total doses of from 0.6 to 2.8 Gm. per kilogram of body weight, and the dye tests were repeated.

It is seen that after the first week's medication with 0.6 Gm. per kilogram, the functional efficiency of the liver for excretion of dye remained about the same as after chloroform in three animals (rabbits 7, 10 and 11), and approached the control levels in three others (rabbits 8, 9 and 12). That is, the cinchophen not only did not aggravate or

increase the injuries to the liver produced by chloroform in the first three rabbits, but appeared to facilitate recovery of the livers from the injuries of chloroform in the other three rabbits. When the total dosage of cinchophen in rabbits 10, 11 and 12 reached 2.4, 2.4 and 2.8 Gm. per kilogram at the end of forty-five, forty-four and fifty-two days, respectively, there was a definitely greater decrease in the function of the liver than after the administration of chloroform in only one rabbit (rabbit 11). In rabbit 10 there was only a tendency to some decrease in functional efficiency, and in rabbit 12, which received the highest dose, or 2.8 Gm. per kilogram, the dye test showed no changes from the control results before medication of any kind.

As for abnormal changes in morphology of the liver, only one (rabbit 10) of the six rabbits in the group given chloroform and cinchophen showed evidences of injury similar to the injury in rabbits 5 and 6, which received cinchophen alone. The changes in rabbit 10 consisted of focal necrosis with hydropic degeneration and nuclear damage. Of the remaining five rabbits in the group given chloroform and cinchophen, the livers of four were examined. Three of the latter (rabbits 9, 11 and 12) showed questionable beginning hepatic degeneration, as indicated by slight to moderate cloudy swelling, after total doses of 0.6, 2.4 and 2.8 Gm. of cinchophen per kilogram, and one liver (rabbit 8) appeared entirely normal after a total dose of 0.6 Gm. per kilogram. The appearances of the livers of these rabbits were not comparable with the injured livers of rabbits receiving chloroform alone (controls in the department of pathology). In the opinion of Drs. Ophüls and Wood, the livers of all of these four rabbits might be considered practically normal, and the slight cloudy swelling present in three instances, would allow complete recovery. At least, it seemed that chloroform, a more or less specific hepatic poison, given in functionally injurious doses, did not demonstrably assist or potentiate the action of large doses of cinchophen so as to result in definite and dependable morphologic injury of the liver. On the contrary, the comparative absence of abnormal morphologic changes in the livers of chloroformed rabbits treated with cinchophen seemed to agree with a restorative action to normal from, or absence of aggravation of, deranged function, according to the dye test used.

The equivalents in dosage of cinchophen and in period of medication for a man weighing 70 Kg., based on the data for the rabbits given chloroform and cinchophen were estimated about as follows: daily chloroform anesthesia, a severe poisoning with all that such action implies, for about two hours, during a period of two months preceding the taking of a total of from 42 Gm., or  $1\frac{1}{4}$  ounces, during a similar following period, to 196 Gm., or over 6 ounces, during the following



one and one-sixth years with practically no, or only questionable, functional and morphologic injury to the liver, if the reactions of human beings and of rabbits are assumed to be the same. These doses might correspond to the therapeutic doses for some chronic conditions, such as arthritis, neuritis and neuralgia, for which a patient might take a little over 7 grains (0.42 Gm.) daily uninterruptedly for one year and two months, and his liver, if healthy, would not be less sound than before such medication. However, it is in cases of chronic illness, perhaps infectious in character, that toxins or metabolic products might conceivably predispose the liver to injury by cinchophen, in ways different from the action of chloroform, and not revealed by its use.

*Phosphorus and Cinchophen* (table 2 and chart 3).—Six rabbits were given daily injections for seven days of fresh solutions of yellow phosphorus in olive oil, of a total for each rabbit of 6 mg. of phosphorus per kilogram of body weight. All the rabbits showed definite though moderate functional injuries, as indicated by the results of the dye tests. Two animals (rabbits 17 and 18) were not given cinchophen, being used as controls for evidences of morphologic injury in the liver, together with other controls in the department of pathology: Both livers showed marked periportal necrosis, cloudy swelling, vacuolization of liver cells, detachment of central cells and fatty and hydropic degeneration, or, in other words, a composite picture of hepatic degeneration. Four others (rabbits 13, 14, 15 and 16) were given cinchophen gastrically in total doses of from 0.6 to 1.6 Gm. per kilogram after the injections of phosphorus. The results of the dye tests in all rabbits approached those in the controls; cinchophen did not aggravate or reduce further the decreased hepatic functional efficiency caused by the phosphorus. The effect of the cinchophen medication might be regarded as beneficial (and it certainly was not injurious), owing to the approach to the normal functional state of the liver. However, the tendency to natural recovery from the injurious effects of phosphorus must be recognized as an important factor in these tendencies toward a normal condition, because the approach to normal occurred in rabbits 17 and 18 without cinchophen medication. Nevertheless, the treatment of phosphorized rabbits with cinchophen could not be regarded as detrimental to the dye-excretory function of the liver.

Interestingly, there was also a comparative absence of morphologic injuries in these livers. For instance, the liver of rabbit 16, which received the highest total dose of cinchophen, or 1.6 Gm. per kilogram, was practically normal, or showed only a slight cloudy swelling. The livers of rabbits 13, 14 and 15 showed only slight to moderate cloudy swelling amounting to slight parenchymatous degeneration, or were practically normal. In fact, the interpretation of the changes presented

great difficulties to the pathologists in their attempt to decide whether these livers should be regarded as pathologic or as normal, because such a change as slight cloudy swelling may easily be an artefact and may be encountered in normal tissues. On the other hand, the livers of two phosphorized animals (rabbits 17 and 18), which were not treated with cinchophen, showed the marked pathologic changes described, as though the absence of cinchophen medication left the hepatic tissue permanently damaged. Accordingly, it is tempting to suggest that there was a correlation of the coincident functional and morphologic changes in the liver under cinchophen when the results indicated approaches to the normal or control state. However, we are inclined to attribute beneficial effects, under the conditions, to spontaneous recovery and repair of the liver.

The equivalents in total dosage of cinchophen and period of medication for a man weighing 70 Kg., based on the data for the phosphorized rabbits, were about as follows: preliminary daily poisoning with injections of yellow phosphorus in total weekly doses of 420 mg. for a period of eight weeks followed by continued medication with cinchophen until a total had been given of from about 42 Gm., or  $1\frac{1}{3}$  ounces, for two months to 102 Gm., or over 3 ounces, for eight months. This would be the equivalent of the daily ingestion of from about 10 grains (0.7 Gm.), or two 5 grain tablets of cinchophen, for two months to about 6 grains (0.4 Gm.), or two 3 grain tablets, for eight months. This would seem a considerable amount of medication to be tolerated by a body already severely injured by a potent poison, namely, phosphorus. Yet, all this might be done without apparent detriment to the liver.

#### EXPERIMENTAL RESULTS OF OTHERS

The results of our own experiments with the feeding and the gastric administration of cinchophen to animals indicate the lack of an adequate experimental basis for clinical cinchophen toxicosis, except possibly the effects of extremely large doses beyond therapeutic possibilities. It was thought desirable, for a more complete treatment of the subject, to consider here the experimental results of others published while our work was in progress. Certain of the results take care of gaps in our own work, such as the limited use of parenteral administration and the omission of the use of dogs, and other results illustrated effects according to other procedures. Most of the other investigators have failed to indicate the equivalents for man of the dosage of cinchophen and the period of medication in their experiments. Thus they have failed to indicate the significance of their experimental results for human medication, except for general statements or opinions of possibilities. These equivalents have been estimated by us and put together with the significant data and results of these authors in a concise summary in

table 3. A short comment on this summary will suffice in view of the correlations with our results already attempted.

Practically all the authors have granted the difficulties of establishing frank injury to the liver with doses of cinchophen within the therapeutic

TABLE 3.—*Summary of Experimental Poisoning and Injury to the Liver from Cinchophen Reported in the Literature*

Animal Species	Route of Administration of Cinchophen	Total Dosage of Cinchophen, Gm. per Kg.	Equivalent Total Dose and Period for a Man* Weighing 70 Kg., Gm.	Fate	Injury to Liver	Comment	Author
White rats	Subcutaneous	1 to 2 (acute)	70-140	Death 24 hrs.	Present (not specific)	Necrosis of other viscera	Reichle <sup>7</sup>
	Subcutaneous	1.6-4 in 8 days	112-280 in 5½ mos.	Killed	Present (not specific)	Cloudy swelling of other organs	
	Subcutaneous	2.6 in 13 days	182 in 8½ mos.	Killed	Present (?)		
	Oral	About 6.2 in 72 days	434 in 4 yrs.	Killed	Absent	Animals starved; livers glycogen-free	
	Oral	About 1.4 in 31 doses; also same for neo-cinchophen	98 in 1½ yrs. (?)	Killed	Absent	Animals starved; livers glycogen-free	
	Oral	About 1.5 (?) in 10 days	105 in 7 mos.	Killed	Absent	Chloroform previously by inhalation and subcutaneously	
White rats (females)	Feeding	3 to 8 in 12 to 32 days	210-560 in 8 mos. to 1½ yrs.	Nearly ½ died; rest, killed	Present	No injury to liver in controls	Knoble and Smith <sup>9</sup>
Dogs	Feeding	5.95-11.9 in 2 and 3 days	416-806 in 10 and 15 days	Killed	Present	Anorexia; gastric ulcers present	Churchill and Wagoner <sup>10</sup>
	Feeding	1.19-1.79 in 2 and 3 days	84-126 in 10 and 15 days	1 died; 1 killed	Present	Anorexia; no gastric ulcers; duodenal diverticulum; dye retention	
	Feeding	2.1 up to 4.2 and 10.5 in 17 days	147, up to 294 and 735 in about 3 mos.	Killed; biopsy	Present (moderate)	Bile absent in urine; recovery from injury to liver on withdrawal of drug	Myers and Goodman <sup>11</sup>
Rabbits	Feeding	21 in 45 days	1,470 in 1 yr.	Killed; biopsy	Present (less than dogs)	.....	Myers and Goodman <sup>11</sup>

\* The following average spans of life have been used in these studies: man, 60 years; dog, 12 years (1 day = 5 days of human life); rabbit, 8 years (1 day = 8 days of human life), and white rat, 3 years (1 day = 20 days of human life).

range. Nearly all claim to have obtained hepatic injuries after excessively large doses given for both short and long periods. Using white rats, Reichle<sup>7</sup> has made one of the most determined efforts to reproduce the injuries to the liver which he had previously<sup>8</sup> found in human

8. Reichle, Herbert S.: Toxic Cirrhosis of Liver Due to Cinchophen, Arch. Int. Med. 44:281 (Aug.) 1929.

autopsy materials, but with essentially negative results. Consequently, he has justifiably concluded that the hepatic injuries seen in clinical cinchophen toxicosis are possibly conditioned by a hypersensitive state. Having failed to obtain specific injury to the liver after parenteral (subcutaneous) administration of enormous total doses, such as the equivalents of from 70 to 140 Gm., or more than from 2 to 4 ounces, given at once, and as much as 280 Gm., or 9 ounces, given in five and one-third months, Reichle investigated the possible prior effects of starvation and rendering of the liver glycogen-free, and of chloroform poisoning, but again with negative results. In the latter experiments, Reichle used oral doses of about the same magnitude as those employed in subcutaneous administration, namely, the equivalents of from 98 Gm., or about 3 ounces, in one and six-eighths years, and 105 Gm., or about  $3\frac{1}{4}$  ounces, in seven months, to 434 Gm., or about  $10\frac{3}{5}$  ounces, in four years. These negative results of Reichle's would appear unsupported by the positive results claimed by Knoble and Smith,<sup>9</sup> Churchill and Wagoner<sup>10</sup> and Myers and Goodman,<sup>11</sup> provided little or no weight is attached to the dosage given. However, some considerations will show that most of these authors used therapeutically prohibitive doses of cinchophen.

For instance, Knoble and Smith fed their rats the equivalent of from 210 to 560 Gm., or from about 7 to 18 ounces, of the drug in from eight months to one and three-fourths years of continuous administration. Nearly one-half the rats died, which indicated the dangerous character of the dosage, and the remainder were killed. The livers were injured in all but the control rats. Churchill and Wagoner fed dogs the equivalents of from 416 to 806 Gm., or from about 13 ounces to over  $1\frac{1}{2}$  pounds, in from ten to fifteen days. Again, these are enormous daily doses, such as a human subject could not tolerate. The livers and gastric mucosae of the dogs were injured, which is not at all surprising. Anorexia and injuries to the liver still occurred as well as one death, but there were no gastric ulcers in dogs which received the equivalent of from 84 to 126 Gm., or from  $2\frac{5}{8}$  to 4 ounces, in from ten to fifteen days. Such large doses probably would never be prescribed for continued medication during such long periods. The daily amounts would correspond to and exceed doses for intensive medication in rheumatic fever, and would cause symptoms of cinchonism and other effects for longer periods than could be tolerated.

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9. Knoble and Smith: *Am. J. Physiol.* **9**:537, 1931.

10. Churchill, T. P., and Wagoner, F. H.: *Proc. Soc. Exper. Biol. & Med.* **28**:581, 1931.

11. Myers, Harold B., and Goodman, Louis: *Cinchophen Hepatitis: An Experimental Study*, *Arch. Int. Med.* **49**:946 (June) 1932.

Myers and Goodman have probably made the most satisfactory attempt at determining the changes in the liver because of the individual character of their controls. They removed surgically portions of hepatic tissue from their dogs and rabbits before giving the cinchophen, during medication and again at the end of it. All their animals were killed; the livers of dogs showed moderate changes, greater discreteness and coarseness of granules in the cytoplasm of hepatic cells and some degree of chromatolysis in the nuclei, which an expert pathologist thought were deviations from the normal. There was no cellular destruction, and no evidence of fat. In rabbits, the changes were still less marked. The changes in the liver in dogs were readily reversible, since withdrawal of the drug resulted in recovery. Bile was absent in the urine at all times. However, the dosage of cinchophen and the periods of medication in the experiments of Myers and Goodman tended to be large, if not excessive. Our estimates indicate the following equivalents for a man weighing 70 Kg.: totals of from 147 to 294 Gm. to 735 Gm., or from 1.6 to 3.3 Gm. to 8.1 Gm. daily for about three months, according to the doses for dogs, and a total as high as 1,470 Gm., or 4 Gm. daily for one year, according to doses for rabbits. The lower levels of these doses (such as 147 and 294 Gm.), which are high and the period of medication, would about correspond to those of some clinical reports, but the highest doses, such as 735 and 1,470 Gm., would be excessive. Yet the abnormalities in the livers were no more pronounced after the highest than after the lowest doses. These considerations leave us somewhat skeptical of the significance of the comparatively slight or moderate abnormalities in the liver, in the absence of functional changes, in the experiments of Myers and Goodman, despite their carefully controlled experiments. Such results have scarcely anything in common with the much more severe changes claimed to exist in clinical toxicoses, which frequently have been fatal. Therefore, they seem to us inadequate and unsatisfactory as an experimental reproduction of the condition in clinical cases.

The net result of our consideration of the results of others is that experimental cinchophen injury of the liver comparable to that reported clinically has not yet been accomplished with doses of cinchophen that come within the therapeutic range, and that a predisposition or sensitization to such injury from the use of hepatotoxic agents has not been demonstrated. Large doses of cinchophen, which probably would not be tolerated and would never be prescribed clinically, can injure the liver to a small and variable extent, but the injuries are not specific or limited to the liver. In fact, they speak for the remarkable resistance of the healthy organ to the drug. In all essential respects, then, the experimental results of others are in agreement with our results, which were

negative, except as already noted. It now remains to comment on matters of general significance connected with the phenomena of experimental and clinical poisoning from cinchophen.

#### COMMENT

Throughout this paper we have insisted on the absence of a demonstrated cause and effect correlation between continued administration of cinchophen and hepatic injuries, such as has been claimed to exist. After the strenuous insistence on such a relationship in the clinical reports, we were disappointed in not being able to discover a correlation in our own experimental results and in those of others. In view of all that has been considered, it seems hardly possible that cinchophen could destroy more hepatic tissue, say 80 per cent or more, than is known to be necessary for the suspension or destruction of hepatic function. And it should be remembered that a fatal outcome in clinical cinchophen toxicosis is common enough to attract attention. Yet, compared with the large doses tried in animals, the clinical doses are small, and the latter would have to achieve the feat of destroying the organ more completely than could the large doses. Obviously the situation is paradoxical. It may be that clinical toxicosis represents something different from the experimental poisoning.

Since in clinical toxicosis from cinchophen there may be, and probably are, conditions beyond control, there is little that can be said. This appears the more true from the fact that similar toxic effects have not been found to follow the use of the drug and of certain conditions together experimentally. On the contrary, this experimentation indicated that there might be an opposite effect on the liver, the condition of which was not made worse, and appeared to be improved, by cinchophen medication. It must be granted, however, that the conditions and injuries used were not necessarily the equivalents of those of the clinical disease. Nevertheless, conclusive proof of the importance of clinical injury or disease in the hepatic injuries associated with cinchophen medication remains to be obtained, even though the potentialities for pathologic changes may be granted. The question is indeed difficult, since it involves so many assumptions regarding mechanisms of the disease and of the drug's action. But for the sake of safety, the possibilities of effects of hepatic injury or disease and of cinchophen on each other ought to be granted.

Aside from the contributory effects of disease, there is no doubt that the continued daily administration of cinchophen in large doses to young growing animals causes stunting of growth, which in itself reflects the production of functional abnormalities, even though the liver is not demonstrably injured. In this respect cinchophen occupies com-

mon ground with many other drugs, such as alcohol, borates, arsenic, fluorides and thallium. The effects are those of chronic intoxication, and their occurrence is not surprising, since all drugs are potentially toxic. None is necessarily injurious, however, if used judiciously.

The important question is whether or not the reported hepatic injuries from cinchophen medication are properly to be attributed to a direct action of the drug when it is used in doses within therapeutic limits and conditions, including the intensive and often repeated doses for antirheumatic medication. From the negative experimental evidence, and from the fact that cinchophen has been used for years with known benefits in different conditions, notably in gout and rheumatic fever, it would seem that the ordinary medication with cinchophen is practically devoid of harm and capable of rendering benefits. Finally, there has been oversight of the fact that clinical cinchophen poisoning is sporadic and capricious, considering the use of the drug under all conditions by hundreds of thousands of people during a score of years. Many physicians have never seen a case of toxicosis from cinchophen. The effects of the large therapeutic doses tried experimentally do not come into consideration in this problem, any more than would doses of similar magnitude of any number of other drugs ordinarily used safely in therapeutics. For instance, the heavy metals used in the treatment of syphilis, such as mercury, bismuth and the arsenicals, can injure and even destroy the kidneys, if used injudiciously, but these drugs are given annually to hundreds of thousands of patients without serious injury. Moreover, the heavy metals, as indeed also many alkaloids, narcotics and other drugs, are potentially far more toxic to viscera than are the cinchophens.

The undesirable consequences of far-fetched strictures on cinchophen medication are the possible deprivation of patients of a useful remedy and the dangers of medicolegal complications resulting from legitimate medication. On the other hand, no one should condone or encourage the uncontrolled or indiscriminate use of, or promiscuous self-medication with, cinchophen or proprietary products containing the drug or its derivatives. But these matters, which unfortunately require frequent reiteration for the sake of sound therapeutic principle and practice, can be emphasized regardless of the toxic potentialities of the drug.

#### SUMMARY AND CONCLUSIONS

1. Clinical cinchophen toxicosis, especially the injury to the liver, has been found to lack an adequate experimental basis establishing a direct relation of cause and effect.
2. Evidences of injuries were absent in white rats under continued medication with large and extratherapeutic doses of cinchophen and

neocinchophen for periods as long as one-ninth the span of life, and practically absent in rabbits which received large doses of the drug gastrically during shorter periods. Bile was absent from the urine of all the animals. The urine of the rats was colored various shades of red, owing to the presence of the drugs or their products, as was demonstrated by positive chemical tests, indicating gastro-intestinal absorption of the drugs.

3. Prior injury of the liver in rabbits by chloroform anesthesia and by phosphorus did not demonstrably sensitize or predispose the liver to, or increase the effects of, cinchophen medication, as indicated by the negative results of a dye test of functional efficiency and by a practically normal histologic picture, or only mild changes, in the tissues of the liver. The apparently beneficial effects of cinchophen on the liver in these experiments are attributed to natural or spontaneous repair and recovery.

4. The results of others, obtained on white rats, rabbits and dogs under different conditions, are believed to be essentially negative, in general agreement with our results, in view of the enormous and therapeutically prohibitive doses of cinchophen, the long periods of medication and the practically absent or mild to moderate histologic changes in the livers as contrasted with the severe, and often fatal, changes in human cases of so-called cinchophen toxicosis.<sup>12</sup>

5. The evidences of slight injuries to the liver in occasional rabbits in our experiments, and the positive claims of some authors using dogs, are outweighed by considerations of the character of the evidence, including the large doses of cinchophen, the effects of which are not specific. For instance, continued treatment of young growing rats with large doses of cinchophen or of neocinchophen caused stunting of growth and loss of body weight, changes which reflect systemic poisoning, but similar effects have been reported for such drugs as ethyl and methyl alcohol, borates, fluorides and thallium.

6. Despite the failure to establish definitely an experimental basis for clinical cinchophen toxicosis, and to predispose or sensitize the liver to cinchophen by more or less specific hepatic poisons, the harmful potentialities of large and continued doses of the drug and of clinical hepatic diseases or injury, and their effects on each other, should be

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12. This conclusion is supported by the concurrence of opinion of several experienced pathologists, expressed in discussions of cinchophen poisoning reported in the *American Journal of Pathology* (7:574, 1932), which came to our attention after this paper was ready for publication. J. S. Davis (*Am. J. M. Sc.* 184:555, 1932) has recently published a study of two hundred patients taking cinchophen and neocinchophen, in a wide range of dosage, without fatalities or clinical evidences of injury to the liver.



recognized. For these and other reasons, the uncontrolled, indiscriminate or promiscuous use of cinchophen, or of products containing it or its derivatives, and especially self-medication, should not be condoned or encouraged. Legitimate and ordinary therapeutic medication, including the intensive treatment for rheumatic fever, given under the direction of physicians, is generally safe and capable of producing well known benefits.

## Book Reviews

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**Dietetics for the Clinician.** By Milton Arlanden Bridges. In collaboration with Ruth Lothrop Gallup. With a Foreword by Herman O. Mosenthal. Price, \$6.50. Pp. 666. Philadelphia: Lea & Febiger, 1933.

Having engaged in full-time hospital work for five years and in postgraduate teaching, the author presents this book to supply a need for more practical and detailed dietary advice than is usually contained either in the textbooks of physiology or in those of medicine. A large number of useful tables compiled from reliable sources are presented, together with many practical dietary suggestions. The numerous menus, as well as a section entitled "Foods from a Culinary Standpoint," are contributed by Miss Ruth Gallup.

Various sections covering the dietary matters affecting the specialties are written by others than the author. An introduction and an excellent section on Bright's disease are by Mosenthal; the subjects of infant feeding and dietetic management of diseases of children are by Saxl. Other contributors and their topics are as follows: Spain, allergy; Lawton, college athletes; Short, diabetes; Blake, dentistry; Blakeslee, epilepsy; Hinton, goiter; Nilsen, otolaryngology; Brenner, surgery; Carter, surgery; Ruppe, tuberculosis; Freund, rectal disease; Marks, vitamins; Townsend, genito-urinary disease; Sherwin, physiology of digestion; Ayres, dermatology, and Hyams, obstetrics and gynecology.

The chapter on vitamins provides an excellent brief review of the subject with interesting emphasis on partial dietary insufficiencies as opposed to the high grade avitaminoses. The recent independent reports of Szent-Györgyi and King with the demonstration that vitamin C is not a derivative of narcotin, as stated, but hexuronic acid, were made presumably too late for inclusion.

The subject of diet is rapidly becoming more important as the newer knowledge of nutrition accumulates, but when one departs from general principles and attempts the prescribing of diets for specific diseases, as in this book, it is impossible to avoid contentious matter. This is recognized by the author. Much of modern diet therapy is pure empiricism without physiologic or laboratory data to confirm or disprove it, and thus it is improbable that any single diet will meet with whole-hearted approval. The authors have attempted to replace tradition by reasoning from general principles, but they fall short, as is admitted, in many cases.

The point of view is a sane one but somewhat less critical than might be desired, particularly in several of the special sections. The Gerson, salt-poor, low protein diet, for instance, is considered as little short of miraculous for everything from tuberculosis, for which it was introduced, to, exophthalmic goiter, pernicious anemia, arthritis, arteriosclerosis and infantilism. Absurdities are probably inevitable in a work of this kind in which many authors with varying degrees of knowledge about nutrition are involved. For instance, it is stated that "fermentable foods because of their tendency to gaseous formation should be limited" after operations on the rectum. Yet among the foods recommended are bread, pies, pastries and candy. One must ask what foods, if not these, are fermentable, also whether the author is informed that intestinal gases arise for the most part not by the fermentation of foods but by secretion into the bowel from the blood. It would be possible to pick numerous similar examples of inconsistency in this book, but no more than one may find in the diet procedure of any one of the leading medical centers. A more serious criticism is the lack of attention to quantitative considerations. A common error in medical practice, and one not avoided in this book, is to consider all men as equal in regard to requirements for food, whereas in this matter at least there is quite accurate information, and one should appreciate the wide variation in the calories required, depending on the size, age and sex of the person.

**The Child and the Tuberculosis Problem.** By J. Arthur Myers, Ph.D., M.D., F.A.C.P., Professor of Preventive Medicine, University of Minnesota; Chief of Medical Staff, Lymanhurst School for Tuberculous Children. With an introduction by William P. Shepard, M.D., F.A.P.H.A., Welfare Director, Western Division, Metropolitan Life Insurance Company. Cloth. Price, \$3. Pp. 230, with 21 illustrations. Springfield, Ill.: Charles C. Thomas, 1932.

Myers reemphasizes the relative importance of tuberculous infection in childhood. He does this in such a way that any layman who is interested in the welfare of the community can understand the source of infection, the accepted means of diagnosis and the essentials in prevention and treatment. The problem of tuberculosis is so bound up with social and economic difficulties that progress in the solution of this problem can be hoped for when every nurse, every social worker and most fathers and mothers are familiar with at least the main facts of this all too common disease.

While the subject is covered in all its various aspects and furnishes an excellent guide, particularly to parents and teachers, one feels a rather wide gap between that part which deals with infection and diagnosis and the relatively emphasized institutional treatment. It has been true in the past, and will probably continue to be true in the future, that most patients with tuberculosis, whether adults or children, will be treated at home. A special chapter dealing with the indications for treatment at home and the details of such treatment could be added with advantage to an otherwise well planned and very satisfactory popular textbook.

#### **Ninth Annual Report of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, 1932.**

Attention is called to the original statement regarding the purposes for which the fund of this foundation would be used: 1. For the present, researches will be favored that are directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery. 2. As a rule, preference will be given to researches on a single problem or on closely allied problems; it is hoped that investigators in this and in other countries may be found, whose work on similar or related problems may be assisted so that more rapid progress may be made possible. 3. Grants may be used for the purchase of apparatus and supplies that are needed for special investigations, and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances. Applications for grants for the year 1933-1934 were to be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, so that they might be in the hands of the Executive Committee before May 1, 1933, and were to include statements as to the character of the proposed research, the amount of money requested and the objects for which the money is to be expended.

**Criteria for the Classification and Diagnosis of Heart Disease.** By the Criteria Committee of the Heart Committee of the New York Tuberculosis and Health Association, Inc. Third edition. Price, \$1. Pp. 131. New York: Tuberculosis and Health Association, Inc., 1932.

Efforts to arrive at a uniform nomenclature and uniform criteria for using the nomenclature have not proved successful in the case of every disease. Particularly is this true of nephritis and arthritis. Numerous classifications of these two diseases have appeared. To date, none is satisfactory; at least, none is catholic. The Criteria Committee of the Heart Committee of the New York Tuberculosis and Health Association, Inc., has been eminently successful in establishing a standard, universally applicable classification for heart disease. This classification is based on clearcut criteria determined by experts after exhaustive study. Only those who have indulged in the tedium of serious statistical endeavor and have

experienced that sense of lack of confidence in their labor because of the inadequacies and variations of faulty nomenclature can fully appreciate this classification.

It is practically fool-proof. It is a concentrated summary of diseases of the heart. Added to this edition is an appendix, consisting of two sections: (1) "A Guide to Radiological Diagnosis in Heart Disease," by Geza Nemet, and (2) "The Criteria for the Interpretation of Electrocardiograms," by Arthur De Graff.

**Traitement médical des ulcères gastro-duodénaux.** By Pierre Oury and J. Mézard. Price, 15 francs. Pp. 54. Paris: Gaston Doin & Cie, 1933.

This small volume presents first a brief discussion of the ulcer syndrome. The authors divide the expressions of gastric ulcer into four types: the dyspeptic or painful form; the hemorrhagic form; the form in which vomiting occurs, and the classic form, which, they add, is decidedly rare. The roentgenologic findings and the laboratory examination are then discussed. The next chapter is devoted to the complications of peptic ulcer; it is divided into six main heads according to the various types of complications that may occur. The last of these complications discussed is that of cancerous degeneration of the ulcer; it is noted that Americans claim that from 40 to 70 per cent of gastric cancers result from preexisting ulcers, whereas the French consider the proportion to be not more than from 3 to 5 per cent. The third chapter is on the diagnosis of the disease, and the succeeding four chapters discuss various types of treatment. The therapeutic advice that the authors give is sane and sensible and adheres relatively closely to the methods carried out in this country. Unusual types of treatment are dismissed with a few critical words, usually rejecting as inadequate the fundamental basis on which such treatments are based. The book is to be commended as a practical exposition of the subject.

**Modern Alchemy.** By W. A. Noyes and W. A. Noyes, Jr. Cloth. Price, \$3. Pp. 197. Springfield, Ill.: Charles C. Thomas, 1932.

Under this alluring title the authors discuss in a brief but entertaining manner the miracles of modern chemistry and medicine. The philosopher's stone was, to be sure, a hoax, but true science has forced from nature not only grander but more picturesque secrets than Cagliostro ever dreamed of. This, in a word, is the authors' thesis—perhaps a little platitudinous—and the metaphor does seem strained when in the final chapter, entitled "The Elixir of Life," one finds brief remarks on the processes of disease, immunity, hormones and the like. The reviewer resents a little the implied slight to the alchemists, since they, after all, only represented art, which should not be compared with or criticized in terms of science; leaving aside, however, these considerations, the book is really an excellent exposition in simple terms of important problems of "natural philosophy" in connection with which developments have been made so quickly that most of us have not kept up. One learns, for example, about the structure of atoms, the chemistry of radioactive substances and electrochemistry, with sidelights here and there on the practical application of this knowledge. The writing is in a pleasant style, and the format is attractive.

**Asthma, Hay Fever and Related Disorders: A Guide for Patients.** By Samuel M. Feinberg. Price, \$1.50. Pp. 124. Philadelphia: Lea & Febiger, 1933.

It is the purpose of the author of this book to furnish a guide for patients suffering with asthma, hay fever and related disorders. He deals chiefly with bronchial asthma, but includes also hay fever, vasomotor rhinitis, cutaneous disorders and other manifestations of allergy. The book includes a brief historical review and a discussion of the etiology, complications and treatment of these disorders. The author has made available to the patient much valuable information concerning the problems of diagnosis and treatment which should promote,

therefore, a much better understanding and cooperation between the patient and the physician. Especially valuable is the discussion of daily contacts with possibly offending proteins, which includes a history of foods and the more common air-borne substances.

A criticism which might be offered is that in the effort to give information of value both to the physician and to the patient, certain phases of the book may perhaps prove too comprehensive for the average patient.

**La néphrite expérimentale à l'urane.** By F.-J. Traissac. Pp. 187. Bordeaux, France: Librairie Delmas Bordeaux, 1933.

Following the injection of uranium nitrate into rabbits there is noted a syndrome which resembles nephritis in man. Grave anatomic alterations are produced in the kidneys. Diuresis, a diminished elimination of phenolsulphonphthalein and acidosis occur. There is a glycosuria (of renal origin). In the urine are albumin and casts; the urea and cholesterol of the blood are abnormally increased. There is also definite evidence of damage to the liver, so that the name "*hépato-néphrite toxique*" is applied. In attempting to explain these phenomena, the author expresses the belief that the damaged liver is responsible for the disturbed metabolism of nitrogen and fat, and that the albumin excreted probably originates in lesions of the liver. The excretion of the albumin depends on alterations in the vessels of the kidney. Observing that the administration of insulin reduces the nitrogen of the blood and the hypercholesteremia in rabbits, Dr. Traissac suggests the possibility of the treatment of nephritis with insulin.

**The Duodenum.** By Edward L. Kellog. Price, \$10. Pp. 855. New York: Paul B. Hoeber, Inc., 1933.

The collection between two covers of information which otherwise must be sought in widely scattered quarters wins the gratitude of every physician. This task Dr. Kellog and his collaborators have achieved in notable form with reference to the duodenum. The reviewer was especially impressed by the chapters dealing with the less common disorders: abnormalities of position, diverticula, fistulas, injuries, hernias and tumors. These subjects are treated in monographic form, with a historical review, abstracts of the literature, case reports and a general discussion. One finds much material which otherwise would have to be laboriously sought in the periodical literature. The sections on anatomy, physiology and methods of study, as well as those on the more common disorders, such as ulcer, are also satisfactory. The volume concludes with a chapter on surgical procedures. The bibliography of about 3,000 titles is carefully selected. Apparently no pains have been spared in making the format attractive, and a rich collection of illustrations enlivens the text.

**The Tides of Life.** By R. G. Hoskins, Ph.D., M.D., Director of Research, Memorial Foundation for Neuro-Endocrine Research; Research Associate in Physiology, Harvard Medical School. Price, \$3.50. Pp. 352. New York: W. W. Norton & Company, 1933.

Many popular books have been written about the glands of internal secretions which are full of fallacies and half truths. Here, however, is a volume written by a recognized authority in a popular vein, so that any one eager to know of the recent fascinating advances in this subject will find it interesting and instructive. The book is well written, the subject matter is interestingly told, and, on the whole, the attitude has been conservative and with an eye to the truth.

To the large reading public interested in the internal secretions and to those who want to learn more of the recent accumulation of knowledge, this book is highly recommended. The author, possibly because of his training as editor of *Endocrinology*, has struck an excellent balance so that scientific facts are shorn of their technicalities but have lost little of their accuracy.

## PRIMARY CARCINOMA OF THE LUNG

WITH SPECIAL REFERENCE TO INCIDENCE, EARLY DIAGNOSIS  
AND TREATMENT

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Owing to the rather large number of recent reports on primary cancer of the lung, another contribution may seem to be an unnecessary addition to the already extensive literature. As we review this subject and reflect on past experiences, we suspect that many cases may have been overlooked owing to a lack of complete understanding or an inadequate study of the material. Particularly was this true a decade or more ago when the disease appeared to be more or less a rarity. Recently there has been a reported increase in cancer of the lung to a figure approaching 2 per cent of all patients coming to autopsy. Wells<sup>1</sup> said, "There seems to be little doubt that primary cancer of the lung is now a more common disease in Europe and America than it was even ten or fifteen years ago." The disease appears to be so common that it behooves every clinician, especially those dealing with conditions of the chest, to keep it constantly in mind. It is therefore because of an obvious need of emphasizing the diagnostic criteria of this condition, as well as of pointing out the desirability and feasibility of early treatment, that we feel justified in the present effort.

### HISTORY

From a historical standpoint, only outstanding developments need be given for the purpose of a better orientation of the subject. Bayle,<sup>2</sup> in 1810, reported three cases of true cancer of the lung as "phthisie cancreuse," and noted diffuse and nodular types. This was the first definite work on cancer of the lung. Laennec,<sup>3</sup> in 1819, led a group

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From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium.

1. Wells, H. G.: Cancer Statistics as They Appear to the Pathologist, *J. A. M. A.* **88**:399 (Feb. 5); 476 (Feb. 12) 1927.

2. Bayle, G. L.: *Recherches sur la phthisie pulmonaire*, Paris, Gabon, 1810, p. 439.

3. Laennec, R. T. H.: *Traité de l'auscultation médiate et des maladies des poumons et du cœur*, Paris, J. A. Brosson & J. S. Chaudé, 1819, vol. 2, p. 295.

of men who described "encaphaloid" of the lung, but he was not able to diagnose it ante mortem. Walsche,<sup>4</sup> in 1843, called it by the name "cancer." In the same year Köhler,<sup>5</sup> in Germany, wrote a monograph on the subject. Bell<sup>6</sup> first diagnosed pulmonary cancer in life from the symptoms of dyspnea, cough, pain and stridor and verified it by autopsy. Stokes<sup>7</sup> first diagnosed it by physical examination and gave a complete description of its clinical manifestations. In 1863, Virchow<sup>8</sup> described the pathologic process of pulmonary tumors, including cancer of the lung, although it was his opinion that primary cancers of the lung were rare. Waldeyer,<sup>9</sup> in 1867, showed the origin from epithelium, although a controversy over the squamous or cylindric cell origin arose soon after and has continued to recent times.

#### INCIDENCE

The incidence of cancer of the lung is a perplexing problem and one about which a variety of opinions exist, many of which are to the effect that it has increased rapidly since the World War. Weller<sup>10</sup> accurately expressed the situation when he said: "No other form of neoplastic disease is more intriguing from the standpoint of incidence than primary carcinoma of the lung, for within a generation it appears to have become one of the common forms of malignant disease instead of the rarity which it was believed to be at the beginning of the century."

The realization of its relative frequency began just prior to the Great War, although various reports have been made from time to time over the last half century. In 1878, Reinhard<sup>11</sup> collected 25 cases of carcinoma of the lung, but by 1891 Werner<sup>12</sup> could find only 9 that were fully verified. Wolf<sup>13</sup> collected 31 in 1895, and Pässler<sup>14</sup> 57 by

4. Walsche, W. H.: A Practical Treatise on Diseases of the Lung, ed. 4, London, Smith, Elder & Co., 1871.

5. Köhler, R., quoted by Wolff, Jacob: Die Lehre von der Krebskrankheit, Jena, G. Fischer, 1911, vol. 2.

6. Bell, J., quoted by Jacob Wolff.<sup>5</sup>

7. Stokes, W.: Diagnosis of Cancers of the Lung and Mediastinum, Dublin M. J. **21**:206, 1842.

8. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863.

9. Waldeyer, A.: Die Entwicklung der Karzinoma, Virchows Arch. f. path. Anat. **41**:470, 1867.

10. Weller, C. V.: Pathology of Primary Carcinoma of the Lung, Arch. Path. **7**:478 (March) 1929.

11. Reinhard, W.: Der primäre Lungenkrebs, Arch. d. Heilk. **19**:369, 1878.

12. Werner, M.: Das primäre Lungencarcinom, Freiburg I. B., H. Epstein, 1891; quoted by Weller.

13. Wolf, K.: Der primäre Lungenkrebs, Fortsch. d. Med. **13**:725 and 765, 1895.

14. Pässler, H.: Ueber das primäre Carcinom der Lunge, Virchows Arch. f. path. Anat. **145**:191, 1896.

1896. In 1911, Adler<sup>15</sup> collected 374, and in 1918, McMahon and Carman<sup>16</sup> stated that there were 428, authentic reports. At present there are several thousand reports on record, and the number has been rising so rapidly that the disease is considered by many to be undergoing an increase.

In arriving at definite information concerning the alleged increase of primary cancer of the lung, we may profitably make comparisons with that of cancer in general, because after all cancer of the lung should be governed by the same laws that govern general cancer. Concerning the latter, we find reliable statistics and many carefully prepared reports, one of the best of which is that of Wells.<sup>1</sup> This author, among other things, stated that "A high cancer death rate is evidence of a good state of public health," and again, "Cancer is probably increasing to just about the extent that people are kept from dying of something else." Although Briese,<sup>17</sup> Egenolf,<sup>18</sup> Bejach,<sup>19</sup> Holzer,<sup>20</sup> and others found no increase, it seems probable that a relative increase should exist as a result of, and proportionate to, an increased life expectancy, and that the recorded incidence will increase with diagnostic zeal and acumen. Many pathologists—Junghanns,<sup>21</sup> Hanf,<sup>22</sup> Breckwoldt<sup>23</sup> and Sonnenfeld<sup>24</sup>—however, report increases, and public health agencies are almost unanimous in this opinion.

The records of the United States Census Bureau<sup>25</sup> for the years 1900 to 1914, inclusive, show for a large number of countries a gradual increase (with the exception of Switzerland) from 15 to 40 per cent. This incidentally was a quiet period of the world's history.

15. Adler, I.: *Primary Malignant Growths of the Lungs and Bronchi*, New York, Longmans, Green & Company, 1912.

16. McMahon, F. B., and Carman, R. D.: *Roentgenologic Diagnosis of Primary Carcinoma of the Lung*, *Am. J. M. Sc.* **155**:34, 1918.

17. Briese: *Zur Kenntnis des primären Lungenkarzinoms, mit statistischen Angaben*, Frankfurt. *Ztschr. f. Path.* **23**:48, 1920.

18. Egenolf, W.: *Ueber die in den Jahren 1921-1927 vom Göttinger pathologischen Institut beobachteten bösartigen Geschwülste*, *Ztschr. f. Krebsforsch.* **31**:396, 1930.

19. Bejach, H. E.: *Beiträge zur Statistik des Carcinomas*, *Ztschr. f. Krebsforsch.* **16**:159, 1917.

20. Holzer, H.: *Zur Frage der Häufigkeit des Bronchialkrebses*, *Med. Klin.* **21**:1235, 1925.

21. Junghanns, H.: *Der Krebs der Lungen, Bronchien und oberen Luftwege*, *Ztschr. f. Krebsforsch.* **28**:573, 1929.

22. Hanf, Dora: *Zur Frage der Zunahme der Lungenkrebse in den letzten Jahren*, *Virchows Arch. f. path. Anat.* **264**:366, 1927.

23. Breckwoldt, R.: *Zur Frage der Zunahme der Lungenkrebse*, *Ztschr. f. Krebsforsch.* **23**:128, 1926.

24. Sonnenfeld, A.: *Klinik des primären Bronchialcarcinoms*, *Ergebn. d. ges. Med.* **8**:546, 1926.

25. U. S. Census Bureau, *Cancer Mortality*, 1914, p. 18.



According to Cumming,<sup>26</sup> the death rate from cancer in the United States increased 50 per cent from 1900 to 1929. Lichty and his co-workers<sup>27</sup> showed an increase of about 10 per cent from 1916 to 1925. As Cumming also stated that between 1900 and 1929 there was a decrease in the death rate from 17.195 to 12.343 per thousand population (39.3 per cent) and an increase in life expectancy to 58 years, we may consistently assume with Wells that the number of persons saved from tuberculosis, typhoid, diphtheria, scarlet fever and measles during early and middle life has been added to the number of those attaining the cancer age, and thus the number of deaths from cancer has been increased almost in the same proportion.

The operation of this shifting of the population into the cancer age is shown in figure 1, taken from figures of the United States Census Bureau, one for 1880 and one for 1928—a period of forty-eight years, after which time about twice as many people are shown to reach the

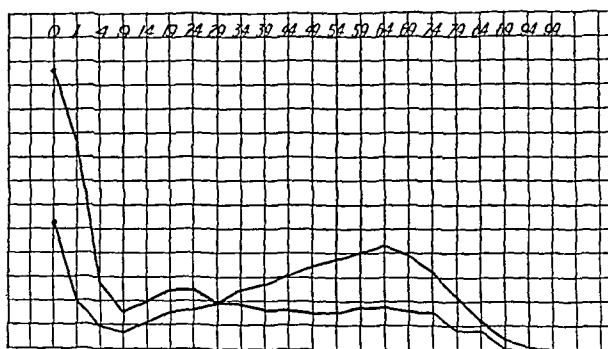


Fig. 1.—Death rate curves for 1880 and 1928, respectively. The curve of 1880 begins high and tapers off gradually toward old age, while the 1928 curve begins lower, drops lowest at about 9 years, crosses the other curve in midlife, and rises to a second peak at 64 years. The people dying formerly in young life are carried over and die in adult life, about twice as many reaching the cancer age.

cancer age as before. This is compatible with an average increase of 24 per cent in cancer in the United States from 1900 to 1914, as revealed by the aforementioned census report.

While one must not be deceived by a decreasing death rate, which may be apparent only as a result of an increased birth rate, the increase in the period of life expectancy is a sure sign of longevity.

In a further attempt to compare cancer of the lung with cancer in general, we have plotted the figures representing most of the larger collections found in German and in English literature that were suitable

26. Cumming, H. S.: *Herald-Tribune Magazine*, New York, Nov. 1, 1931.

27. Lichty, J. A.; Wright, F. R., and Baumgartner, E. A.: *Primary Cancer of the Lung*, *J. A. M. A.* **87**:144 (July 17) 1926.

for charting. Kikuth,<sup>28</sup> Brandt<sup>29</sup> and Biberfeld,<sup>30</sup> among others, have already shown such charts. Three other representative authors have been selected at random when several sets of figures are given at different periods of time, and the findings have been listed in figure 2. *A* shows the findings of Junghanns<sup>21</sup> of Dresden; *B*, those of Assmann<sup>31</sup> of Leipzig, and *C*, those of Holzer<sup>20</sup> of Prague. Three sets of figures have been plotted with three curves each, all of which are explained in the legends. The relatively high figures of two of these (as well as other authors at the beginning of the century) cause us to wonder if the reported increase in cancer of the lung, based on autopsies, may not be due more to human fallibility in diagnosis or some other factor than to a true increase. With these various points in mind, we have

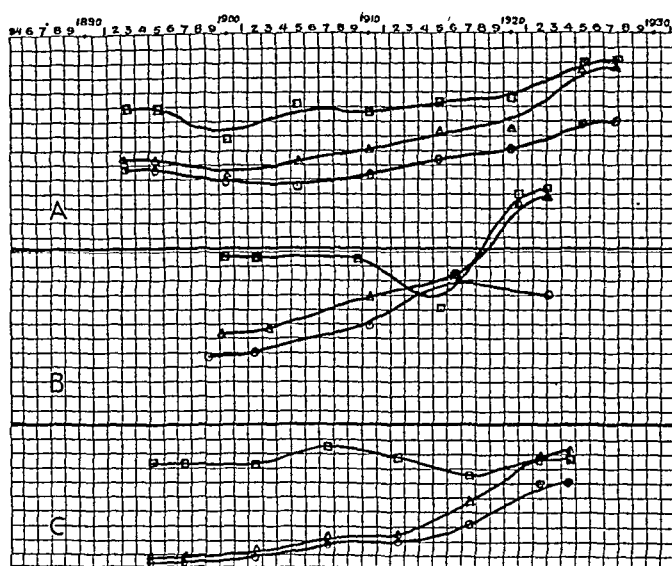


Fig. 2.—Relation of cancer of the lung to general cancer: *A*, findings of Junghann of Dresden; *B*, of Assmann of Leipzig, and *C*, of Holzer of Prague. The curves marked with squares represent the general cancer in percentage of all autopsies; each line rise equals 1 per cent. The curves marked with triangles represent cancer of the lung in tenths of per cent; each line rise equals 0.1 per cent. The curve marked with circles is the percentage ratio of cancer of the lung to cancer in general.

charted in figure 3 approximate curves of twenty-one authors from various parts of the world.

28. Kikuth, W.: Ueber Lungencarcinom, Virchows Arch. f. path. Anat. **255**:107, 1925.

29. Brandt, M.: Ueber primäre Lungentumoren in Riga, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:74, 1926.

30. Biberfeld, H.: Zur Statistik und Klinik der Lungengeschwülste, Med. Klin. **22**:1353, 1926.

31. Assmann, H.: Zur Frage der Pathogenese und zur Klinik des Bronchialkarzinoms, Med. Klin. **20**:1757 and 1796, 1924.

In addition to Junghanns<sup>21</sup> and Assmann,<sup>31</sup> Duguid<sup>32</sup> of Manchester, England, Breckwoldt<sup>23</sup> of Hamburg, Katz<sup>33</sup> of Heidelberg and Lipschitz<sup>34</sup> of Zwickau have always obtained rather high results, but reported a further increase nevertheless. Some reveal a depression from about 1912 to 1918 (perhaps due to the war when attention was more or less diverted). Katz,<sup>33</sup> Kikuth,<sup>28</sup> Hanf<sup>22</sup> and Biberfeld<sup>30</sup> showed this depression. Others included are Wolf,<sup>13</sup> Fuchs,<sup>35</sup> Reinhard<sup>11</sup> and Pässler<sup>14</sup> (all before 1895), who showed a very low percentage; Zacherl,<sup>36</sup> who has used some of the same figures presented

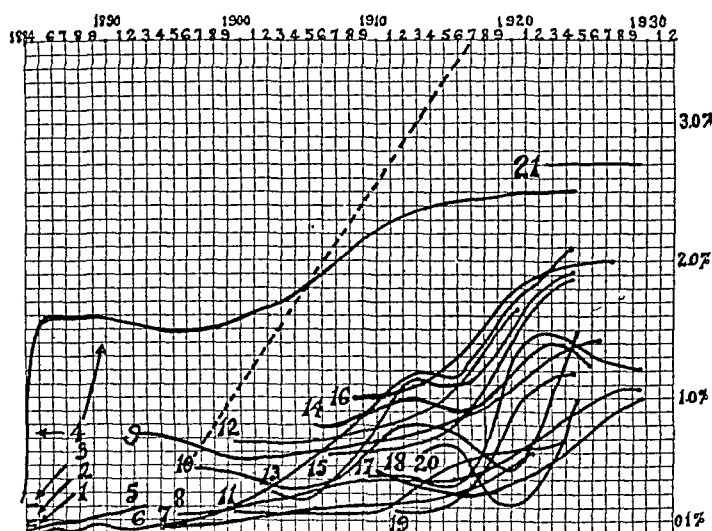


Fig. 3.—Increase in cancer of the lung, expressed in percentage of all autopsies by various men: 1, Reinhard; 2, Fuchs; 3, Wolf; 4, Duguid; 5, Pässler; 6, Kikuth; 7, Holzer; 8, Zacherl; 9, Junghanns; 10, Biberfeld; 11, Stachelin; 12, Seyfarth; 13, Hanf; 14, Katz; 15, Simpson; 16, Lipschitz; 17, Berblinger; 18, Rosahn; 19, Sonnenfeld; 20, Breckwoldt, and 21, Buschbeck. Note the "depression" during the World War and the sharp increase afterward. The heavy broken line represents the improvement in diagnosis, expressed in percentage, as given by Ferenczy and Matolcsy, Weller and Lubarsch for different periods beginning in 1896 with 5 per cent and ending in 1925 with 47.5 per cent correct diagnoses.

32. Duguid, J. B.: Incidence of Intrathoracic Tumors in Manchester, *Lancet* 2:111 (July 16) 1927.

33. Katz, K.: Statistischer Beitrag zur Kenntnis des Lungencarcinoms, *Ztschr. f. Krebsforsch.* 25:368, 1927.

34. Lipschitz, M. A.: Ueber die Zunahme des Bronchialkarzinoms im letzten Jahrzehnt, *Deutsche med. Wchnschr.* 55:1708, 1929.

35. Fuchs: Beiträge zur Kenntnis der primären Geschwulstbildungen in der Lunge, Inaug. Diss., Munich, 1886; quoted by B. M. Fried.

36. Zacherl, S.: Ueber das primäre Lungenkarzinom, *Wien. klin. Wchnschr.* 44:967, 1931.

before by Ferenczy and Matolcsy;<sup>37</sup> Seyfarth,<sup>38</sup> Staehelin,<sup>39</sup> Simpson-Levy,<sup>40</sup> Rosahn,<sup>41</sup> Berblinger<sup>42</sup> and Buschbeck.<sup>43</sup> No pretense is made at completeness, although most of the large collections have been included (fig. 3).

In order to be more absolute, we selected the most important complete sets of figures of European authors for a thirty-four year period, tabulated the total figures by year in the accompanying table and charted them in figure 4. These figures include only complete years, so they

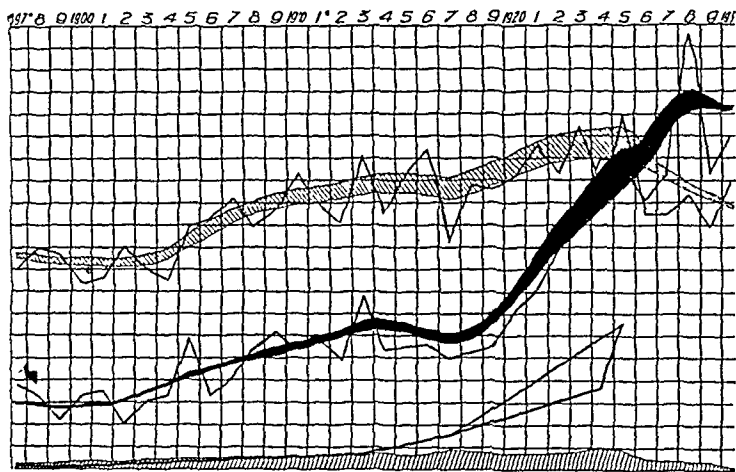


Fig. 4.—The aggregate of general cancer and cancers of the lung (table 1) in the most important complete reports. The top barred band (along the irregular curve) represents the ratio of general cancer to all autopsies (each large square represents 1 per cent). The width of the band represents approximately the number of hundreds for each small square per year. The black band is the same for cancers of the lung except that the quantity is one tenth of the other. The barred band at the bottom represents the total autopsies expressed as thousands for each small square per year. The black curve ending in a triangle represents a few reports expressing the percentage of correct diagnoses of cancers of the lung. It begins at about 5 per cent in 1897 and ends at about 50 per cent in 1925.

37. Ferenczy, K., and Matolcsy, T.: Ueber das primäre Lungenkarzinom, Wien. klin. Wchnschr. **40**:618, 1927.

38. Seyfarth, C.: Lungenkarzinome in Leipzig, Deutsche med. Wchnschr. **50**:1497, 1924.

39. Staehelin, R.: Ueber die Zunahme des primären Lungenkrebses mit Bemerkungen über die Diagnose, Klin. Wchnschr. **4**:1853, 1925.

40. Simpson-Levy, S. L.: Primary Carcinoma of the Lung, Quart. J. Med. **22**:413, 1929.

41. Rosahn, P. D.: Incidence of Primary Carcinoma of the Lung, Am. J. M. Sc. **179**:803, 1930.

42. Berblinger, W.: Zunahme des Lungenkrebses und Staublungenkrankheiten, Med. Klin. **27**:1337, 1931.

43. Buschbeck, H.: Ueber die Häufigkeit des primären Lungencarcinoms, Ztschr. f. Krebsforsch. **34**:678, 1931.

may not coincide exactly with those given in the respective reports. They include 79 cases of Berblinger,<sup>42</sup> 71 of Kuhn,<sup>44</sup> 100 of Katz,<sup>33</sup> 47 of Breckwoldt,<sup>23</sup> 79 of Sonnenfeld,<sup>24</sup> 198 of Biberfeld,<sup>30</sup> 129 of Schlesinger,<sup>45</sup> 245 of Kikuth,<sup>28</sup> 200 of Hanf,<sup>22</sup> 89 of Lipschitz<sup>34</sup> and 136 of Buschbeck.<sup>43</sup>

In all there are 1,355 cancers of the lung and 22,712 cancers in 185,434 autopsies. By adding the redistributed figures of Junghanns,<sup>21</sup>

*Aggregate Figures of Important Complete Reports of Cancers, Cancers of the Lung and Total Autopsies from 1897 to 1930, Inclusive*

Year	Total Number of Autopsies	Total Number of Cancers	Percentage of Cancers in Relation to All Autopsies	Total Number of Cancers of Lungs and Bronchi	Percentage of Cancers of Lungs and Bronchi in Relation to	
					All Cancers	All Autopsies
1897.....	2,417	218	9.0	9	4.1	0.38
1898.....	2,700	270	10.0	9	3.3	0.33
1899.....	2,800	270	9.7	6	2.2	0.22
1900.....	3,406	283	8.3	11	3.8	0.33
1901.....	3,084	266	8.6	11	4.0	0.35
1902.....	3,000	300	10.0	6	2.0	0.20
1903.....	4,278	387	9.0	13	3.4	0.30
1904.....	4,198	355	8.5	14	3.9	0.33
1905.....	4,459	488	10.9	17	3.5	0.38
1906.....	4,829	543	11.3	16	2.9	0.33
1907.....	5,019	613	12.2	20	3.2	0.40
1908.....	4,934	542	10.9	27	5.0	0.54
1909.....	5,481	641	11.7	34	5.3	0.62
1910.....	5,713	758	13.3	39	4.0	0.65
1911.....	6,156	734	11.9	37	5.0	0.38
1912.....	6,693	743	11.1	33	4.5	0.49
1913.....	5,784	816	14.1	45	5.5	0.78
1914.....	7,403	851	11.5	40	4.7	0.54
1915.....	6,021	804	13.3	35	4.2	0.55
1916.....	6,683	963	14.4	37	3.9	0.56
1917.....	8,848	899	10.2	33	3.7	0.50
1918.....	8,006	1,026	12.8	50	4.8	0.62
1919.....	7,212	908	12.6	40	4.4	0.56
1920.....	7,154	943	13.2	51	5.4	0.72
1921.....	7,049	1,030	14.6	56	5.4	0.80
1922.....	7,298	1,072	13.3	71	7.0	0.98
1923.....	8,191	1,266	15.4	98	7.7	1.19
1924.....	9,809	1,227	12.5	102	8.3	1.40
1925.....	8,858	1,404	15.9	130	9.2	1.50
1926.....	4,805	551	11.5	58	10.6	1.21
1927.....	4,558	524	11.5	67	12.9	1.47
1928.....	3,776	467	12.4	74	16.0	1.96
1929.....	3,546	384	10.9	47	12.3	1.33
1930.....	1,266	166	13.0	19	11.4	1.50
Total.....	185,434	22,712	12.2	1,355		

Probst,<sup>46</sup> Holzer,<sup>20</sup> Derischanoff<sup>47</sup> and Zacherl,<sup>36</sup> who gave the numbers in five year periods, the results were almost identical, giving a total

44. Kuhn, C.: Symptomatologie des primären Bronchialcarcinoms, Ztschr. f. Krebsforsch. **31**:276, 1930.

45. Schlesinger, M.: Bronchialcarcinome von 1924-1929, in Leipzig, Ztschr. f. Krebsforsch. **31**:517, 1931.

46. Probst, R.: Häufigkeit des Lungencarcinoms, Ztschr. f. Krebsforsch. **25**:431, 1927.

47. Derischanoff, S.: Zur Statistik und Genese des Lungenkrebses, Ztschr. f. Krebsforsch. **35**:481, 1932.

of 2,359 cancers of the lung and 38,338 cancers in 359,389 autopsies, perhaps half of all cancers of the lung reported to date.

These figures and charts reveal a gradually increasing incidence of general cancer of around 65 per cent over the thirty-four years with a depression during and after the war. There is also an increasing incidence of cancer of the lung that is greater than the incidence of general cancer until the war; then, after a slight depression, there is a tremendous rise, the peak being reached in 1928, amounting to a tenfold increase. Since then there has been a tendency to decrease. Corresponding to this rise, however, is an increase in the diagnoses of cancer of the lung, as given by certain authors, from 5 per cent in 1896 to about 50 per cent in 1925. With careful work, it should approach 75 per cent at the present time. General cancer is entirely different. The diagnosis in this group should have been well over half correct throughout the whole thirty-four year period. Instead of a tenfold increase in diagnoses, as with cancer of the lung, there is no more than a 10 or 15 per cent increase.

It may be contended that an increase in diagnoses should have no effect on figures based on autopsies, but it will tend to bring more cancers of the lung to autopsy and to increase the figures based on autopsies at the expense of the greater group of cancers of the lung that do not come to autopsy. Furthermore, the tendency to more hospitalization, better transportation, better training of physicians during the war and a better appreciation of medical aid on the part of the returned soldiers will increase the recorded incidence without affecting the true incidence of cancer of the lung.

The causes of the increase in diagnosis of cancer of the lung are many and variable. In this regard, one must bear in mind that the discovery of the tubercle bacillus in 1882 permitted a vast number of patients to be separated from those definitely tuberculous and has made further search for diagnosis necessary. It has been our observation that tubercle bacilli are found in all but a trivial minority of active, advanced cases of pulmonary tuberculosis.

The discovery of the x-rays in 1896, with their far-reaching application in medical diagnosis in the last twenty years, has also established the diagnosis of cancer of the lung in many patients whose disease would otherwise have been classed as some other condition.

The use of opaque substances (iodized poppy seed oil 40 per cent), bronchoscopy, pneumothorax, thoracoscopy and bronchoscopic section have all added to diagnostic equipment until over 75 per cent of the diagnoses of cancer of the lung today are, or should be, correct, while less than a decade ago Staehelin,<sup>39</sup> Kikuth,<sup>28</sup> Wells,<sup>1</sup> Grove and Kramer<sup>48</sup> and

48. Grove, J. S., and Kramer, S. E.: Primary Carcinoma of the Lung, *Am. J. M. Sc.* **171**:250, 1926.

others reported not over 35 per cent correct diagnoses. Ferenczy and Matolcsy<sup>37</sup> reported 5 per cent correct diagnoses from 1896 to 1900, 28.4 per cent from 1917 to 1925 and 50 per cent in 1925. In Lubarsch's series, the correct diagnoses totaled 52 per cent in 1920. In 1913, Weller reported only 11 per cent in a collected series of 90 cases. These figures show a marked improvement in diagnosis as years go by.

This same principle applies to nearly all internal or "inaccessible" cancers, although the incidence of external cancers has changed little—in fact, the death rate from external cancer has decreased.

More important than any other factors, however, is the change in pathologic diagnoses. Pathologists have varied their attitude toward the nature of cancer of the lung, thereby placing many cases in this group that were formerly considered to be some other condition. As pointed out by Fried,<sup>49</sup> a dictum of Virchow pervaded the field for a long time. Virchow was of the opinion that the tissue which was subject to metastatic growth rarely produced primary growth, and the lungs were cited as an example. Only a few scattering reports came from the early writers, and perhaps not until Virchow's great influence began to wane did the subject again become open to unbiased investigation. Many of the cancers found in the lungs were formerly considered to be metastases because they are chiefly located at the hilus, where metastases commonly occur. Many were also considered as mediastinal tumors.

One of the greatest changes, however, from the pathologists' point of view, was due to a better understanding of the origin of the undifferentiated cells in cancer of the lung, many of which were formerly considered sarcomatous.

Some of the small cell and even the "oat cell" types may have been considered as sarcomas. In Hunt's<sup>50</sup> series of 26 cases, 21 were of the "oat cell" type. Then many were perhaps considered mediastinal tumors (lymphosarcomas, thymomas and similar tumors) without careful histopathologic analysis. So one sees that it is not only an improvement in diagnoses, but the change of erroneous diagnoses in a relatively small group of cases that come to autopsy that may well have produced a tremendous change in the apparent incidence of cancer of the lung.

#### ETIOLOGY

Only slightly less complicated than the problem of the incidence is that of the etiology. About the only thing definite is that the cause seems to be similar to that of cancer elsewhere. A complete analysis

49. Fried, B. M.: Primary Carcinoma of the Lung, *Medicine* **10**:373, 1931.

50. Hunt, T. C.: Pulmonary Neoplasms, *Lancet* **1**:759 (April 13) 1929.

of the etiology of cancer has been given by Eggers.<sup>51</sup> Most cancers are known to be related to some form of irritation, yet there are a large number that cannot be accounted for on this basis.<sup>51a</sup> "Inherent predisposition" seems to play a rôle, but nothing definite is known so far as human cancer is concerned.

There may be a subtle depletion of some necessary elements in food or other factors that may be gradually undermining normal development. Wells brought up such a question when he said, "Perhaps there are changes in the incidence of cancer independent of the increased age level of the population." Otherwise there is no evidence of increase except that caused by the increased life expectancy and possibly by irritation from radioactive dust (Schneeberg and Joachimstal miners) or by influenza, which plays an uncertain rôle at present.

*Occupation.*—As to the occupation, there seem to be few instances in which there is any relation to cancer of the lung. Claims have been made that automobile gas, smoke, irritating dusts and tar on roads are contributing causes, but in an analysis of a large number of case histories we were unable to find a tendency in favor of any occupation, trade, profession or station of life. Laborers, office workers and housewives are most affected, but they are likewise the most numerous. Mechanics, automobile workers, painters, stokers and carpenters are involved about in proportion to their numbers. Perhaps the only instances in which the occupation may be suspected are the cases occurring in certain European mines. Incidence of cancer of the lung was shown by Arnstein<sup>52</sup> to be high in the workers in the Schneeberg mines, but not in the surrounding population. Schmorl<sup>53</sup> and others studied the problem and reported that arsenic is present in high proportions in the dust of these mines. The dust is also said to be radioactive. Pirchan and Siki<sup>54</sup> showed this in a study of the pitchblende mines of Joachimstal, Bohemia, across the mountains from Schneeberg. These are medical curiosities, however, and produce no great public health problem. Other minerals, such as nickel, cobalt and bismuth have also been accused, but they do not seem to cause any effect when mined elsewhere in the world.

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51. Eggers, H. E.: Etiology of Cancer, Arch. Path. **12**:983 (July) 1931.

51a. Since this work was prepared, McNally (Am. J. Cancer **16**:1502, 1932) has shown that cigaret smoking has increased nearly forty-fold from 1905 to 1931, which increase parallels the rise in cancer of the lung. Certainly this type of irritation must not be disregarded.

52. Arnstein, A.: Ueber den sogenannten, "Schneeberger Lungenkrebs," Wien. klin. Wschr. **26**:748, 1913.

53. Schmorl, G.: Ueber den Schneeberger Lungenkrebs, Verhandl. d. deutsch. path. Gesellsch. **19**:192, 1923.

54. Pirchan, A., and Siki, H.: Cancer of Lung in Miners of Jachymov, Am. J. Cancer **16**:681, 1932.



*Disease.*—The effect of chronic pulmonary disease often seems to be closely related to cancer of the lung. Miller and Jones<sup>55</sup> and Hunt<sup>50</sup> reported that 50 per cent of their patients gave a history of pulmonary involvement. Winternitz and his co-workers<sup>56</sup> and Askanazy<sup>57</sup> studied the after-effects of influenza and pointed out that the regeneration of the epithelium after the disease is peculiar and suggested a possible origin of cancer of the lung, although Heuper<sup>58</sup> could find no relation in the influenza epidemic of 1890 to an increase in cancer of the lung. Ewing<sup>59</sup> stated that tuberculosis is a possible factor, while others report asthma, chronic infections, bronchiectasis, syphilis and chronic pneumonia in the histories. None of the diseases reported with the possible exception of influenza yield any greater proportion of cancers of the lung than the relative incidence of the respective diseases themselves. Perhaps tuberculosis yields much fewer cancers in proportion, owing to its predominance in the young, and all the other diseases must occur during the cancer age before a cancer results. It seems that some yet unknown factors (such as the laws governing mutation) may underlie the whole problem with irritation merely initiating or hastening the process.

#### AGE, RACE AND SEX INCIDENCE

The age incidence of cancer of the lung is not greatly different from that of other cancers, perhaps the patients are a few years younger. In averaging the ages in 112 cases from the reports of Miller and Jones,<sup>55</sup> Hunt,<sup>50</sup> Grove and Kramer,<sup>48</sup> Fried,<sup>49</sup> Fishberg and Rubin<sup>60</sup> and Moise,<sup>61</sup> we found the result to be 49.9 years.

There do not seem to be any racial differences, although Cooper<sup>62</sup> stated that cancer of the lung may be more common in Jews. It seems to depend largely on the type of population. In New York City there

55. Miller, J. A., and Jones, O. R.: Primary Carcinoma of the Lung, *Am. Rev. Tuberc.* **21**:1, 1930.

56. Winternitz, M. C.; Smith, G. H., and McNamara, F. F.: Epithelial Proliferation Following the Intrabronchial Insufflation of Acid, *J. Exper. Med.* **32**:205, 1920.

57. Askanazy, R.: Ueber die Veränderungen der grossen Luftwege besonders ihre Epithel-Metaplasie bei der Influenza, *Cor.-Bl. f. schweiz. Aerzte* **49**:465, 1919.

58. Hueper, W.: Primary Gelatinous Cylindrical Cell Carcinoma of the Lung, *Am. J. Path.* **2**:81, 1926.

59. Ewing, J.: *Neoplastic Diseases*, ed. 2, Philadelphia, W. B. Saunders Company, 1922.

60. Fishberg, M., and Rubin, E. H.: Carcinomatous Abscess of the Lung, *Am. J. M. Sc.* **178**:20, 1929.

61. Moise, T. S.: Primary Carcinoma of the Lung, *Arch. Int. Med.* **28**:733 (Dec.) 1921.

62. Cooper, D. A.: Primary Carcinoma of the Lung, *M. Clin. North America* **12**:1109, 1929.

no doubt will be a high percentage of Jews, but so in England there will be more Anglo-Saxons. Our studies revealed that in American statistics the various races were represented about in proportion to their respective populations.

The incidence of cancer of the lung is higher in the male than in the female, the ratio being about 3:1. This is similar to conditions prevailing with primary cancer of the liver, Hodgkin's disease and perhaps many other malignant forms of disease. The female sex seems to have a greater predilection for cancer of the breast and the genital organs and thus contributes its quota from these specialized organs, because in the statistics of all cancers both sexes are about equally represented, as is well shown by Briese.<sup>17</sup>

*Location.*—Slightly more cancers occur in the right than in the left lung. Brunn<sup>63</sup> added 252 cases to Adler's<sup>15</sup> 374, and reported 283 cancers in the right to 246 in the left lung, 26 in both lungs, 3 of doubtful location and 68 cases in which the location was not mentioned. In the 112 aforementioned cases that we studied, there were 58 in the right lung, 50 in the left lung and 4 in both lungs. There were 24 in the right upper lobe and 17 in the left upper lobe, most of which perhaps originated from the main bronchi. There were 20 definitely in the right main bronchus region with 21 in the left, while only 14 were in the base of the right lung, with 12 in the base of the left lung. None were reported in the middle lobe.

#### PATHOLOGY

The pathologic process will be dwelt on only briefly because this is primarily an epidemiologic and clinical paper. Grossly, there is much difference of opinion regarding the classification, and there is little relationship between the gross and the microscopic findings. The majority of the tumors are nodular masses along the main bronchi, mostly showing at the hilus. There is a much smaller group of an infiltrating type (including the so-called alveolar type) that spreads rapidly and many times resembles lobar pneumonia in the gray state of hepatization. The miliary type frequently mentioned is not common and should, furthermore, be suspected of causing metastases until it has been proved that they are not present.

#### HISTOGENESIS

The time-honored classification of the histology of cancer of the lung is based on the supposed origin from bronchial epithelium, mucous glands and pulmonary alveoli. This has undoubtedly been suggested

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63. Brunn, H.: Primary Carcinoma of the Lung, Arch. Surg. **12**:406 (Jan.) 1926.

by appearances of the cells in the tumor and not from any consideration of the genesis of these cells. If the cells were uniformly of one type, this grouping might not have been questioned, but many times there exist several types of cell in the same specimen, namely, columnar cells with and without mucus, all shades of undifferentiated cells and sometimes squamous or cuboidal types mixed in.

The trend of opinion seems to be veering toward the suggestion of Moise,<sup>61</sup> Fried<sup>49</sup> and others that the tumors arise from the undifferentiated cell layers of epithelium, and the end-result depends on the power remaining in these multipotential cells to differentiate. Some remain undifferentiated, others become columnar, others squamous and others mixed, depending on the individual cell and its environment during the stage of early abnormal development. MacCarty,<sup>64</sup> as early as 1915, pointed out the same thing with reference to all epithelial new growths.

#### METASTASES

Metastasis may occur early or late in the disease. Adler found it mentioned in 280 of 374 case reports. Some tumors show none, even though there may be extensive tumor formation in the lung, while a small primary tumor may localize early in distant organs. As we shall show later, distant metastasis depends largely on the growth of tumor into the pulmonary vein. The adjacent lymph nodes are first involved, with the pleura and liver in close succession. Fried has reported about 30 per cent metastasis to the central nervous system, shown clinically and verified by operation or by autopsy. Kikuth<sup>28</sup> also reported similar figures. Miller and Jones,<sup>55</sup> in a review of 808 cases, gave the following order of percentages of metastases: pleura, 35.2; lymph nodes, 30; liver, 30; lung, 21; kidneys, 15.9; bones, 10.1; suprarenal glands, 9.7; brain, 9.5; heart and pericardium, 2.7; gastro-intestinal tract, 1.1; spleen, 0.7, and muscles, 0.2. The pleural metastases are chiefly due to direct extension; metastases to the lymph nodes may be by the lymphatics or by direct extension, while the other metastases are chiefly hematogenous, from an invasion of the pulmonary vein.

#### COLLATERAL FINDINGS

One of the most common pathologic changes is bronchiectasis, and this is a secondary process. It is due to a closure of the bronchi by occlusion or by pressure. Commonly abscesses or cysts result in the occluded bronchi. Nearly always after occlusion there is a collapse of the tissue of the lung, and this atelectasis frequently gives the appearance of a dense lobar involvement (case 5).

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64. MacCarty, W. C.: Histogenesis of Cancer of the Stomach, *Am. J. M. Sc.* **149**:469, 1915.

## DIAGNOSIS

*Clinical Considerations.*—If there is to be any advance in the diagnosis and treatment of cancer of the lung, it will depend largely on a better realization of the early symptoms and physical findings. While, as Ewing has stated, there is no one factor that is pathognomonic, all taken together generally form a clear picture. This is especially true for those who have learned how to interpret the various symptoms.

With this in mind, we have departed slightly from the usual method of describing the symptomology by considering it in three classes, viz.: early, moderate and advanced. The early symptoms are the ones that need to be stressed, because they are the only ones that will lead to a diagnosis sufficiently early to save the patient's life. We cannot stress this fact too strongly. After the disease has passed the operable stage there is little difference whether the diagnosis is made one year or one month before death, except for the personal satisfaction of the physician.

Without question, the most common early symptom is the cough, with or without expectoration. It usually precedes all others by weeks or months. We prefer to consider the cough and the sputum together, because each alone is of little help, whereas together they may reveal much. If the cough is nonproductive or if it fails to respond to treatment with rest, it is important. A "brassy" or pressure cough is important, but such a cough usually comes after other symptoms (such as dyspnea) have become prominent, and it is present in any other condition when pressure exists. The same statement may be made of cornage—a tubular wheeze or blow. A persistent cough with no sputum or with a blood-tinged mucoid sputum free from tubercle bacilli affords the best early diagnostic evidence. Such sputum should be subjected to a searching study for the appearance of cancer cells, and the patient should have a careful bronchoscopic and roentgenologic study.

Although Weller<sup>10</sup> found sputum next in frequency to cough, its greatest importance is when it is absent in the presence of cough. As there is nothing characteristic about the sputum except that it is scant, mucoid, blood-tinged and free from the ordinary infectious agents, it seems fitting to discuss it as we have done in conjunction with cough. The "current jelly" sputum is not often found, but is of great importance. Different types of hemoptysis or of streaking of the sputum with blood are of far greater importance, especially in the absence of tubercle bacilli.

The coexistence of cancer and tuberculosis in the lungs, incidentally, offers one of the most perplexing problems in the diagnosis of conditions of the chest. The two sets of symptoms must be analyzed separately with attention to the smallest details suggestive of each

disease. If they are coincident in duration, an early separation is practically impossible.

As cough is the most frequent, so pain has the most definite significance, although it is not so common or so commonly found first. It is usually associated with moderately advanced or with far advanced symptoms. When present, it is likely to be outstanding in its character and duration. Owing chiefly to its involvement of the pleura, it may be an intense soreness, a dull, persistent ache, or an excruciating agony that even narcotics will not relieve. The last-named quality is important, because it sharply differentiates this type of pain from that in infections and pleurisy and from most other pains in the chest. Such a characteristic pain is rarely found sufficiently early to be of aid in prognosis.

The third leg of the important triad is composed of symptoms due to pressure (chiefly dyspnea), which usually mark the presence of advanced disease. They are later even than pain, but are characteristic, because few other conditions produce dyspnea or stertorous breathing so early.

In the compilation of figures on the basis of the first appearance of symptoms from the 112 case reports previously mentioned, cough was found mentioned as first (occasionally with some other symptom) 66 times; second, 11 times; third, not at all, and fourth, once. Pain was first or with some other symptom 36 times; second, 15 times; third, 4 times, and fourth, 3 times. Dyspnea was first 14 times; second, 16 times; third, 6 times, and fourth, 6 times. Frank hemorrhage appeared as a rule still later, occasionally at the terminal stage. It appeared first, however, in 5 cases; second in 9; third in 8, and fourth in 5. Blood-streaked sputum was of far greater importance. The sputum was negative in 21 cases and contained tubercle bacilli in 1. The other findings were of no particular significance, except when tumor cells were present following sloughing. As this occurred late in the disease, it is of uncertain value. Anorexia is rarely mentioned but is no doubt common. From the loss of appetite and toxemia there would be loss of weight and weakness, both of which occur late in the disease and are of limited value in diagnosis. Fever and night sweats depend on attendant infection. The absence of fever is more significant than its presence. The effects of circulatory disturbance (clubbing of fingers, cyanosis and similar symptoms) are variable and of little diagnostic value. Although pleural effusion is frequently reported, it is usually late. Its importance depends chiefly on the confusion its presence may cause in differentiating cancer of the lung from tuberculosis. Usually such effusions are tinged with blood or are bloody, especially late in the disease, but not infrequently they are serous, in which case they are difficult to distinguish from the effusions of tuberculosis.

Symptoms from metastases cause the greatest confusion of all and when detected are of little value. Their frequency in the central nervous system has been emphasized by Fried. They manifest themselves by simulating almost any type of tumor of the central nervous system. Pain in the extremities, back or neck or swelling in the neck not infrequently obscures the source of the trouble. Some of the less common symptoms are venous engorgement in the veins of the neck and chest, dysphagia, recurrent laryngeal paralysis, inequality of the pupils and hoarseness.

*Physical Findings.*—The physical findings do not lend themselves readily to classification because of the diversity of the gross pathologic process and the varying stages of the disease. There are some features, however, that are of great significance and help to complete the evidence of tumor. Most important is the appearance of symptoms due to a mass in the thorax such as limitation of motion, changed vocal fremitus, dulness or flatness on percussion, changed breath sounds above and below the tumor and various other signs. In the series of 112 cases from the literature that we analyzed, the physical findings, when mentioned, conformed in general to these conditions. When the pathologic process was chiefly outside the chest or when there were severe complications, the signs were confusing. It is obvious that the physical signs are not clearcut, because rarely were they emphasized or described accurately. In general, we tried to select the earliest diagnosis, which sometimes was made quite late in the course of the disease. Instead of the findings being specified, one will find in the reports "infiltrative lesions," "signs of a mass" and similar diagnoses. Dulness was mentioned 74 times; diminished breath sounds, 58 times; moist râles, 43 times; limitation of motion, 35 times; bronchial breathing, 28 times, and flatness, 16 times. There is no doubt that flatness was present many times without being mentioned. It should be present nearly always late in the disease.

There is no point to listing the many other physical findings, because they have all been mentioned a few times, depending on the pathologic process. For example, amphoric breathing was mentioned 11 times and is often present when there are excavated lesions. Hyperresonance above the mass was mentioned 9 times; distended veins in the neck, 7 times; Virchow's nodes, 4 times; other lymph nodes, 13 times, and enlarged liver, 8 times.

*Roentgenologic Findings.*—Perhaps no other one factor has been so important as the roentgenogram in contributing to the changed attitude toward cancer of the lung. Densities that could be coordinated with the symptoms and physical findings helped to point out primary

conditions in the lung, when without the roentgenographic evidence the diagnosis might have been something else. McMahon and Carman,<sup>65</sup> in 1918, expressed such a sentiment, and at that time they considered cancer of the lung to be a rare condition. They mentioned three gross types—a diffuse, a nodular and a mixed. The diffuse type shows one or more areas of increased density along the roots of the larger bronchi, homogeneous or mottled with indefinite borders extending into atelectatic tissue of the lung; the density at the hilus is not increased or may be wedge-shaped with the apex toward the hilus. The nodular type shows many varying sized nodules throughout the lung, but, as Weller has recently warned, such a type must be suspected of causing metastases until it has been proved that they are not present. Christie<sup>65</sup> emphasized the gradual extension of a tumor of the hilus outward with discrete blending into normal or atelectatic tissue of the lung, although there are many atypical forms. Kornblum<sup>66</sup> pointed out the desirability of early and frequent examination in order to follow the development. It is not always possible to do this, because many times the first picture shows complete obliteration of one whole side.

Miller and Jones have also made a worthy attempt to classify the various lesions from a combined clinical and roentgenologic point of view.

*Bronchoscopy.*—As the x-rays were the first important diagnostic aid, the bronchoscope is the most recent and the most definite in the information it renders. We feel that no thoracic clinic should be without a bronchoscopic service. There are two features of this service: one the direct endoscopic view, and the other the biopsy.

Jackson and his associates<sup>67</sup> pointed out the clear picture presented by the endoscopic view. There is a loss of elasticity of the affected bronchus, or as they described it, a fixed and “woody” tube in the case of a malignant growth. This may be present even when it is not possible to obtain a section. McCrae and his co-workers<sup>68</sup> described clearly the various appearances of bronchial tumors. They may be nodular, papillomatous or simply constrictive, and usually a pearly gray, but many are papillomatous, vascular and pinkish.

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65. Christie, A. C.: Diagnosis of Primary Tumors of the Lung, *Am. J. Roentgenol.* **8**:97, 1921.

66. Kornblum, K.: Case of Primary Carcinoma of the Lung, *Am. J. Roentgenol.* **18**:230, 1927.

67. Jackson, C.; Tucker, G.; Clerf, L. H.; Lukens, R. M., and Moore, W. F.: Bronchoscopy as an Aid to the Thoracic Surgeon, *J. A. M. A.* **84**:97 (Jan. 10) 1925.

68. McCrae, T.; Funk, E. M., and Jackson, C.: Primary Carcinoma of the Bronchi, *J. A. M. A.* **89**:1140 (Oct. 1) 1927.

The section removed may not always be cancerous and should not be relied on entirely. If it is cancerous, there will be no difficulty in making a pathologic diagnosis. The tumor may be deep in the parenchyma of the lung, however, without extending into the bronchi.

Thoracoscopy has been used, but it adds little that may not be learned earlier and by other simpler means, unless the tumor is pleural. In that event, it may be of certain aid.

*Laboratory Examination.*—The diagnosis of cancer of the lung from laboratory data is disappointing outside of the study of the section. No findings are definite, except perhaps the negative ones. Sputum or pleural fluid that is negative for tubercle bacilli is important, however. The presence of malignant cells in sputum and pleural fluid is indefinite, and many times the large alveolar-like malignant cells may be overlooked. If mitotic figures are found, of course, this is more definite. Blood-tinged or bloody pleural fluid free from tubercle bacilli is very suggestive, but it is rarely found until late in the disease. In one of our cases the large alveolar type of cell was thought to be an atypical monocyte or lymphocyte.

*Summary.*—The diagnosis of cancer of the lung without a biopsy is difficult. It requires an interpretation of all the symptoms and findings. The history of cough, with slight blood-streaked sputum free from tubercle bacilli, gradually increasing pain of a permanent nature and increasing dyspnea form the chief diagnostic triad. Signs of increasing growth of the tumor with its symptoms of pressure, toxemia and metastases are the remaining findings.

The physical signs depend on the stage of the disease. In the early stages there are usually suppressed breathing beyond the tumor, limited motion on the side of the tumor, hyperresonance above, bronchial or harsh breathing with some scattering moist râles, and gradually increasing signs of development of the tumor, with dulness and flatness on percussion.

The roentgen picture shows the presence of a small tumor along one of the main bronchi away from the hilus, gradually spreading to involve the whole lobe or lung. A bronchoscopic view reveals a "woody" or fixed bronchus with protruding walls or grayish nodules. Biopsy of a specimen of the involved tissue shows malignant cells.

#### DIFFERENTIAL DIAGNOSIS

The most common and important condition to be differentiated from cancer of the lung, particularly in our work, is tuberculosis. We feel that in the past many persons with cancers of the lung have been sent to sanatoriums and have died, supposedly with tuberculosis. This was especially true before the discovery of the tubercle bacillus and the



x-rays. Lawrason Brown and his associates<sup>69</sup> stated that there should be only 2 per cent error in diagnosis in cases with two of the five cardinal symptoms of tuberculosis (râles in the upper third part of the chest; pleurisy with effusion, hemoptysis, parenchymatous lesion demonstrated roentgenographically and tubercle bacilli in the sputum), if such lesions are unaccounted for otherwise. Of this 2 per cent, we feel that a sizable percentage may be cancer of the lung, because the cardinal symptoms of tuberculosis may be simulated by it, even to the associated presence of tubercle bacilli. Points of greatest difference of tuberculosis are the history, age, hectic afternoon fever, characteristic roentgen picture and physical findings (râles) in the upper part of the lungs, early weakness and loss of weight and the presence of the tubercle bacilli in the sputum or pleural fluid. When cancer becomes associated with the tuberculosis, there is usually the appearance of a grave, painful, progressive disease, with characteristic roentgenographic findings added to those of tuberculosis. A cancerous pleural fluid is usually but not always hemorrhagic. Should the two diseases be simultaneous, there is no way known to us of making an early diagnosis of the cancer.

We shall merely mention other conditions that must be differentiated from cancer of the lung, leaving the details for the textbooks of medicine. Such diseases are: mediastinal tumors, malignant and benign; tuberculosis of the hilar lymph nodes; Hodgkin's disease; carcinoma of the esophagus; sarcoma of the mediastinal structures, including the thymus; aneurysm of the aorta; pneumoconiosis (first stage); foreign body; abscess of the lung; bronchiectasis; acquired atelectasis; massive collapse; cystic lung; chronic pneumonia; echinococcus cysts; benign tumors; chronic passive congestion; substernal goiter; bronchomycosis; blastomycosis; coccidioidal granuloma, and actinomycosis.

#### REPORT OF CASES

CASE 1.—J. P., aged 40, an Austrian waiter, gave a history of influenza at 7 years of age, and a "cold" before admission to the sanatorium, from which he never recovered. There was a cough with slight mucoid sputum, but never bloody; pain later developed along the left side of the spine, which became severe. The appetite was variable; the patient became weak, lost weight, had a slight fever, occasional night sweats and was dyspneic.

On physical examination (Dr. Ludwig), the skin was atrophic and icteric; there was bilateral limitation of motion and flatness, dullness in both upper quadrants, bronchial breathing on the right side, a few moist râles bilaterally and a friction rub between the seventh and the ninth dorsal vertebrae posteriorly, where the patient complained of pain.

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69. Brown, L., and Hayes, J. N.: *Pulmonary Tuberculosis*, in Tice, Frederick: *Practice of Medicine*, Hagerstown, Md., W. F. Prior Company, Inc., 1920, vol. 2, p. 361.

The roentgenogram (Dr. Barber) revealed a solid mass extending out from the left hilus, which was considered to be an abscess, with a linear density in the right lung running diagonally across the field.

Laboratory examination did not reveal any tubercle bacilli; spirochetes and fusiform bacilli were found, but malignant cells were not recognized in a hemorrhagic fluid after tapping. There was a mild secondary anemia, but all other findings were practically negative.

The patient became progressively worse and died.

Autopsy performed on Feb. 23, 1923, revealed that the essential gross pathologic process, a large, white, tough (scirrhous) tumor mass measuring about 15 cm. across, surrounded the left main bronchus below the bifurcation; the left pleural cavity was completely encased in a tumor mass ranging in thickness from 1 to 3 cm.; the rest of the lung contained a few nodules and was atelectatic. The hilar lymph nodes were enlarged and contained tumor tissue. The right lung was enveloped in a fibrous veil that was concentrated in one place to a true bony structure 1.5 cm. across running diagonally for 15 cm. There were many small tumor nodules in this lung. Metastases were present in the hilar lymph nodes, pleura, opposite lung, kidneys, suprarenal glands, gallbladder and stomach. The brain and cord were not examined.

The diagnosis was a scirrhous carcinoma of the left main bronchus of an undifferentiated cell type.

*Comment.*—This case represents one of the most common types of cancer of the lung—a gradually spreading mass coming off a main bronchus, extending to the pleura and metastasizing rather widely. The disease manifested itself first as a bronchial irritation with symptoms of "cold"; then as it spread pain appeared, followed by symptoms of pressure. All findings, physical, roentgenologic and laboratory, were compatible with the pathologic process. The history of influenza thirty-three years before, we feel, was of little importance. The diagnosis was made at autopsy.

CASE 2.—H. K., aged 39, of Polish ancestry, born in Chicago, had been a baker, a marine and during the latter part of his life a clerk. His past history was unimportant. The onset of his condition was influenzal nine months before death, with cough, fever, variable blood-streaked sputum, followed by pain in the right side, with weakness, some night sweats, loss of weight and pleural effusion.

Physical examination (by Dr. Weissman) revealed a well developed but poorly nourished man, with a lagging in the right side of the chest, dulness of the base of the right lung anteriorly and posteriorly, bronchophony in the upper part of the right lung with fine râles, a few fine râles over the upper part of the left lung also, and diminished breath sounds over the base of the right lung.

Roentgenographic examination (by Dr. Cook) revealed fluid at the base of the right lung, with a dense process at the hilus which was thought to be a tuberculous lymph node, perhaps an old tuberculous empyema. There was no mention of a malignant condition.

Laboratory examination showed the sputum to be negative for tubercle bacilli; the effusion contained hemolytic streptococci, but no cancer cells were found. A mild secondary anemia was present (3,900,000 red blood cells), and there was leukocytosis (27,850 white blood cells). All other tests gave negative results.

Autopsy, performed on Feb. 25, 1927, revealed that the essential gross pathologic process was confined to the right lung. It weighed 2,100 Gm., including the diaphragm. The lung appeared to be covered by a fibrous layer 18 mm. thick. This layer became thicker toward the base and measured 12 mm. over the diaphragm. On cut surface, the visceral pleura on its anterior surface was 9 mm. thick. There was a cavity containing 500 cc. of sanguinopurulent fluid located in the base of the pleural cavity. In the lower lobe toward the base was a generalized saccular bronchiectasis. There was a similar condition in the upper lobe at the apex and the hilus. The upper lobe was made up of a large cystic cavity 6.5 cm. in diameter, which shaded off below into numerous similar smaller cavities. Along the left main bronchus 1.5 cm. from the bifurcation was a tumor that almost closed the bronchus and that extended downward and outward into pulmonary tissue toward the middle lobe. The left hilar glands also contained some tumor tissue. The tumor was firm, had the consistency of cartilage and measured 10 cm. at its thickest point, and almost encircled the bronchus. Out in the parenchyma there were much thickening and sloughing. No metastases were found beyond the hilar lymph nodes. The brain was not examined.

The microscope revealed a nonhyalinizing squamous cell carcinoma.

*Comment.*—The influenzal symptoms at the onset of the patient's illness were important, but it is a question whether they were a result or a cause. It is one mode of onset of cancer of the lung, as pointed out by Hunt. There was a marked fibrous pleuritis that may have been due to an infection, concurrent with or preceding the influenza.

There was no suggestion of a malignant growth in the diagnosis until late in the disease, when it was considered, but it was not established until autopsy.

CASE 3.—L. H., aged 46, born in Germany, came to the United States at 1 year of age, and in recent years worked as helper on a brick truck. The history was essentially unimportant. The onset of the condition was a pain in the right side of the chest, followed by cough, expectoration, which was sometimes blood-streaked, weakness and loss of weight. The sputum increased and became foul-smelling.

Physical examination (by Dr. Henrichsen) revealed a flat chest, poor expansion and increased breath sounds in the upper right side with crackling râles in both lungs. The patient was too sick to be examined satisfactorily.

The roentgenograms taken on July 11, 1927, revealed erosion of the fourth and fifth dorsal vertebrae "most certainly malignant." A dense shadow was seen in the right side of the chest in which a peculiar excavation was considered to be "actinomycosis or malignancy." On July 25, the roentgenologic examination showed that beginning about the fifth interspace on the right side and following the costal grill up to and including the apex and along the right border of the spine there was an area of increased density, annular in type, with an area in the midportion that showed aerated lung tissue. This was a rather peculiar looking shadow which had the appearance of a markedly fibrotic wall as though at some time there had been fluid. It had not the characteristic appearance of a pulmonary abscess or of the usual thickened pleura. It was thought that this might represent tuberculosis, but it was held to be unusual in this type. It was stated in the report that occasionally malignant or infectious processes produce similar findings, and that endothelioma, actinomycosis or malignant growth might produce such a condition.

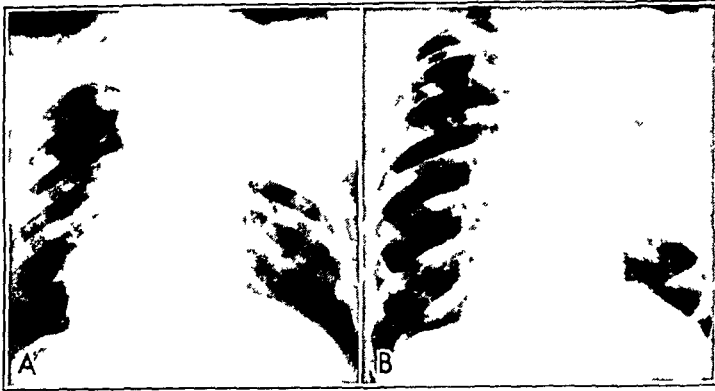


Fig. 5 (case 3).—*A*, roentgenogram taken twenty-two days before death, showing involvement of the right upper lobe by a complete consolidation resembling a massive tuberculosis ("lobite" of Bernard) or abscess. *B*, roentgenogram taken eight days before death, showing an extensive and rapidly excavated carcinomatous abscess with a thick wall.

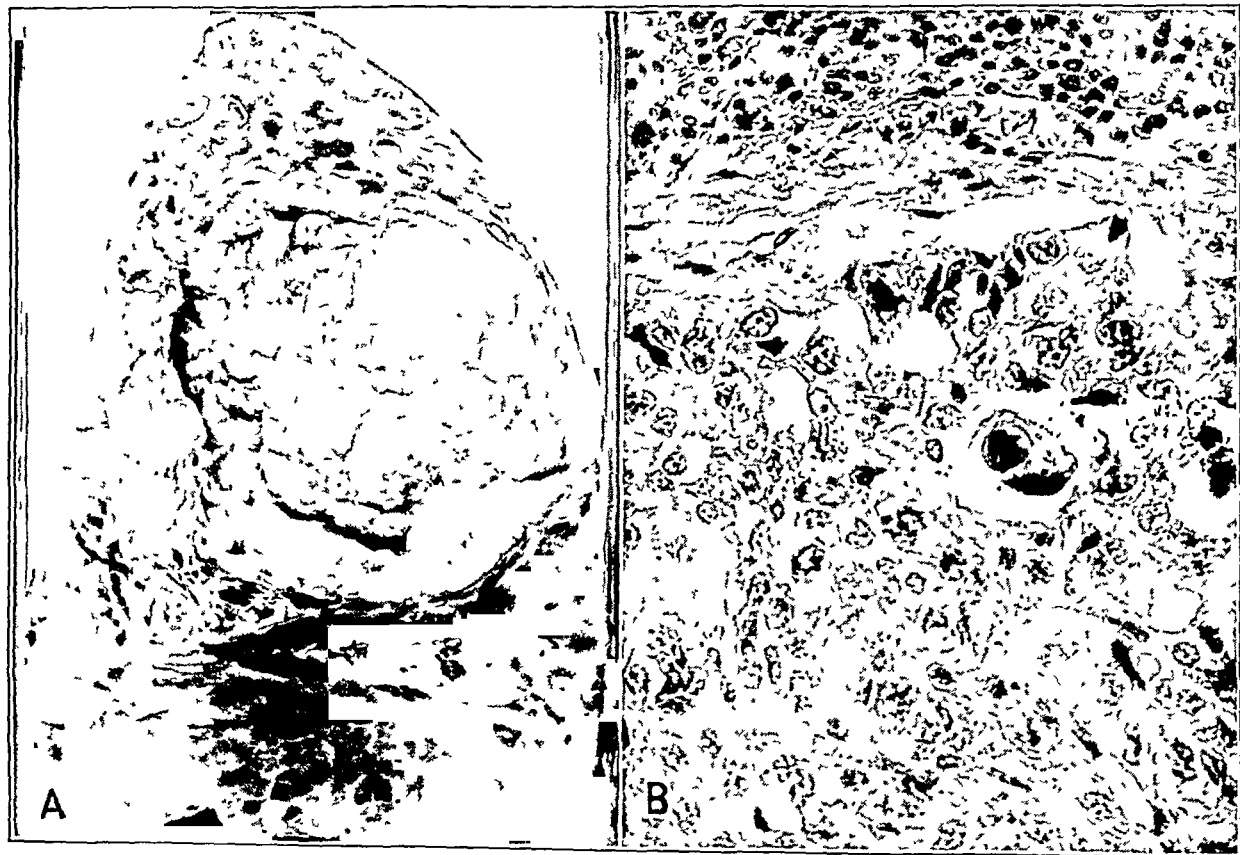


Fig. 6 (case 3).—The gross and microscopic appearance, respectively, of the right lung. Note the excavated abscess (*A*) and the nonhyalinizing squamous cancer cells (*B*). Hematoxylin and eosin stain;  $\times 330$ .

The sputum was always negative for tubercle bacilli, and did not show fungi or cancer cells. There was marked secondary anemia (3,000,000 red blood cells and 10,600 white blood cells). All other tests were negative.

Autopsy, performed on Aug. 2, 1927, revealed a large carcinomatous abscess of the right lung, with a cavity measuring 3 by 4 inches (7.6 by 10.16 cm.), of a nonhyalinizing squamous cell cancer. Metastases were present in the right fifth rib, fourth dorsal vertebra, liver, left kidney, right suprarenal gland and mesenteric lymph nodes.

*Comment.*—This case represents the carcinomatous abscess well shown by Fishberg and Rubin.<sup>60</sup> It is only an advanced stage of the common massive type that has undergone necrosis and sloughing. There is no fundamental reason to class such abscesses as a separate group, but it is convenient from clinical and roentgenologic standpoints. The involvement of the spine seems to be by direct extension through the pleura, because a large tumor nodule connected the tumor of the lung with that in the spine, although there also may have been a growth into a pulmonary vein that may have accounted for it. The diagnosis was made both clinically and roentgenologically, but was not established until autopsy.

CASE 4.—D. M., aged 60, an Irish-American motorman of "moderate" habits, gave a history of pulmonary involvement four years before his death that was called a "touch of pneumonia." Afterward there had been frequent colds, moderate cough, moderate expectoration, hemorrhage a year after the first attack, a dull aching pain in the left side of the chest, gradual loss of weight, moderate dyspnea, moderate weakness and marked night sweats.

Physical examination (by Dr. Rennick) revealed a lagging in the left side, dulness throughout the left lung and the upper part of the right lung, with harsh breath sounds in both lungs and suppression of breath sounds over the base of the left lung. Fluid was suspected but not found at this time, and there were no moist râles. Later, a malignant condition was suspected when the sputum continued to be negative. Still later, a positive specimen of sputum reversed the decision.

Roentgenologic examination (by Dr. Cook) revealed an erosion of the fifth dorsal vertebra which was "questionably tuberculous, and probably malignant." A haziness was noted throughout the left lung, which was dense at the base and decreased toward the apex, with a "shadow in the region of the aortic knob." There was a slight haziness in the apex of the right lung also. The condition of the lung was considered at first "undoubtedly tuberculous," but later it was considered probably tuberculous with pleurisy.

Laboratory examination showed the sputum to be continually negative for tubercle bacilli for the first three months; then one positive specimen was found. The other laboratory findings were of little consequence or were negative. There was a leukocytosis of 23,700 and 4,700,000 red blood corpuscles.

In the subsequent course the patient gradually became worse; all symptoms became exaggerated, and a paraplegia developed in the lower extremities with cystitis. The temperature rose to 101 F., and the patient died.

Autopsy, performed on Feb. 21, 1928, revealed that the essential pathologic process was confined to the lungs. The right lung contained a small tuberculous

cavity with several healed tubercles in the upper lobe. The left lung was quite dense throughout. Cut sections through the bronchi and lung showed a tumor mass in the left bronchial wall. This mass extended for a distance of 6 cm., infiltrating the surrounding lung tissues for varying distances, and extended posteriorly to infiltrate into the visceral pleura. There was a marked bronchiectasis in the lung below the tumor and a considerable amount of caseation throughout the tumor mass which may have been tuberculous. The infiltration was not so dense as usual. The color was a gray black, and the growth was spongy.

At the fifth dorsal vertebra there was a tumor mass connecting with the pleura that extended into the interspace between the fourth and fifth dorsal vertebrae, eroding and infiltrating through the centrum of the fifth vertebra and the intercartilaginous disk. This mass extended to the edge of the spinal canal but not into it.

There were no metastases other than those mentioned. The type of cell is "oat cell" or squamous cell type.

*Comment.*—This is one of four cases of cancer of the lung associated with some form of tuberculosis. It is difficult to make a diagnosis of such a combination. The only means available are to look for the appearance of characteristic shadows of cancer on the roentgenogram and to confirm it with the bronchoscope. In the onset of cancer of the lung associated with a moderately advanced tuberculosis the patient rather suddenly begins to show the symptoms of a grave, unrelenting process that is not like the fluctuating course of tuberculosis, but directly downward without any sign of remission. It was also the second case in succession with metastasis to the spinal cord, which caused the symptoms that led to a definite diagnosis. Here again it may have resulted from a penetration of a pulmonary vein, although this was not demonstrated. The diagnosis was in doubt clinically, but when the metastases appeared in the spine the roentgenogram was definite.

CASE 5.—J. J., aged 44, a Polish-American tailor, smoked heavily and drank moderately, but otherwise his history was unimportant. His illness was of influenzal onset twenty months before death, followed by severe pains in the chest, and was diagnosed as heart disease. There was a slight cough and loss of weight. Nine months before death an intense pain developed on the right side of the chest. Hemoptysis and expectoration then occurred, and later night sweats appeared.

Physical examination by Dr. Rosenbloom revealed a sallow-skinned white man with a phthisical habitus. Lagging was present in the right side, impaired resonance in the upper part of the right lung, harsh breath sounds and a few fine râles at the apex. A malignant condition was suspected. Later, the right side of the chest and neck became swollen, and the veins became engorged. All reflexes and sensations below the sixth dorsal vertebra gradually disappeared.

Roentgenologic examination by Dr. Cook revealed the entire field of the upper part of the right lung to be hazy and dense, with a compression of the bronchus, "probably pneumonic—primarily tuberculous." No pathologic process was found in the dorsal vertebra around which a compression myelitis originated.

Examination of the sputum was always negative for tubercle bacilli. All other laboratory tests were negative except that at times a mild leukocytosis was shown. Bronchoscopic smear from the right bronchus did not reveal any tumor cells. After compression of the cord, laminectomy was performed (by Dr. Thomas) with removal of a tumor, which proved to be metastatic carcinoma.

Autopsy performed on Sept. 16, 1929, showed the following pathologic changes: The bronchus leading to the right upper lobe was obstructed by a soft gray mass measuring about 10 cm. in diameter. Below this, the mass spread out in all directions into the right upper lobe. Distal to this, the bronchi were distended and filled with greenish-yellow pus which accumulated in small and large cavities with thin necrotic walls. The bronchi stood out prominently and caused a marked infiltration about them.

The glands in the right tracheobronchial region and all the posterior mediastinal glands were composed of soft white tissue in which there were smaller yellowish areas.

The trachea and the right bronchus contained small nodular elevations composed of the same soft white material.



Fig. 7 (case 5).—*A* roentgenogram of a right upper lobe showing massive involvement (similar to case 3 but without excavation). *B*, photograph of gross specimen, showing bronchial tumor in eparterial bronchus and a huge mass above, causing compression atelectasis of the pulmonary tissue.

From the level of the fourth to the ninth dorsal vertebra there was a soft, spongy purulent mass occupying the spinal canal. Above this the spinal cord and the dura appeared intact. Below it the spinal cord was soft and the dura slightly discolored. Over the dura in this region and at the place where the lamina had been removed in a previous operation, there were masses of firm yellowish-white tissue resembling the mass in the lung. The spinal column in this region was made up of softened and necrotic bone, pressure on which allowed the escape of reddish-brown purulent material.

Metastases were found in the mediastinal lymph nodes, vertebrae, spinal cord and peripancreatic lymph nodes. The involvement of the cord caused a compression myelitis.

*Comment.*—This case is much like case 1, except that the involvement was in the right upper lobe and there was a metastasis to the spine, apparently by the blood stream. It was the third in succession involving the spinal cord. The cell resembled an "oat cell," but such a designation

has no significance, because there are all shades of differences in the undifferentiated cell. The diagnosis was made by laminectomy, and not by any pulmonary signs or symptoms. Even the bronchoscopic examination failed to yield definite evidence. There was a tumor mass in a smaller pulmonary vein extending into the upper lobe.

Another important feature of this case was that by roentgenographic and physical signs the right upper lobe appeared to be completely consolidated, while the gross pathologic process revealed a tumor of the hilus extending outward about half way to the pleura with only collapsed lung in the remaining portion.

CASE 6.—A. W., aged 50, an American barber, with no history of cancer, but a history of both gonorrhea and syphilis, was treated for syphilis two years

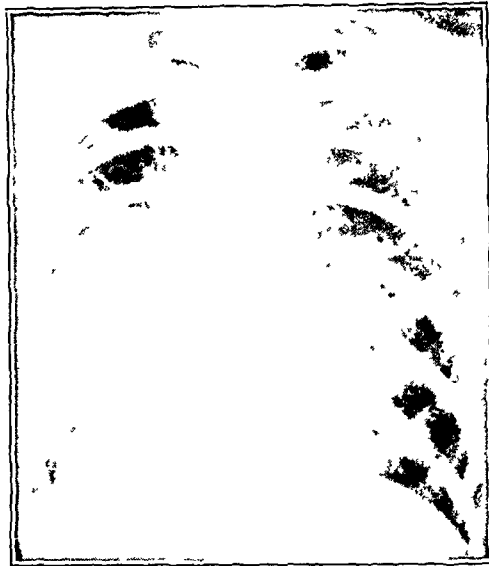


Fig. 8 (case 6).—Roentgenogram in case 6, taken seventeen days before death, showing a mass coming out from the hilus of the left lung.

before admission to the hospital. The Wassermann reaction had been positive, however, for twenty years. Seven years before admission he had a resection for gastric ulcer. The onset of his illness was with a "cold" in 1921, which developed into a typical tuberculosis. The patient entered the Cook County Hospital, where the sputum was found to be positive for tubercle bacilli. There was no fever or night sweats. His complaints on entering the sanatorium were of cough, expectoration, weakness, loss of weight and nocturia, all of which seemed to indicate a tuberculous process on an old syphilitic infection.

Physical examination by Dr. Weissman revealed the following abnormalities: The chest was emphysematous with retraction above and below the clavicles. There was impaired resonance on the right side and over the left base. The diagnosis was tuberculosis with possibility of carcinoma.

Bronchoscopy was suggested but was never done.

A roentgenologic examination by Dr. Cook revealed slight haziness in the upper part of the right lung and "several annular shadows on the root of the left lung which had the density of a glandular structure commonly seen in



lymphatic lymphoma." Four months later Dr. Cook reported that the root of this lung revealed a "well defined haziness with the appearance of a pneumonic process." He suggested that a malignant condition be considered. The right upper lobe showed "evidence of an old tuberculosis."

The laboratory examination revealed one specimen of sputum positive for tuberculosis, also 4 plus Wassermann and Kahn reactions and 39 mg. of non-protein nitrogen per hundred cubic centimeters of blood. Otherwise, the examination gave essentially negative results.

The subsequent course showed that during the last six months of life when the mass was developing in the region of the root of the left lung, the patient's

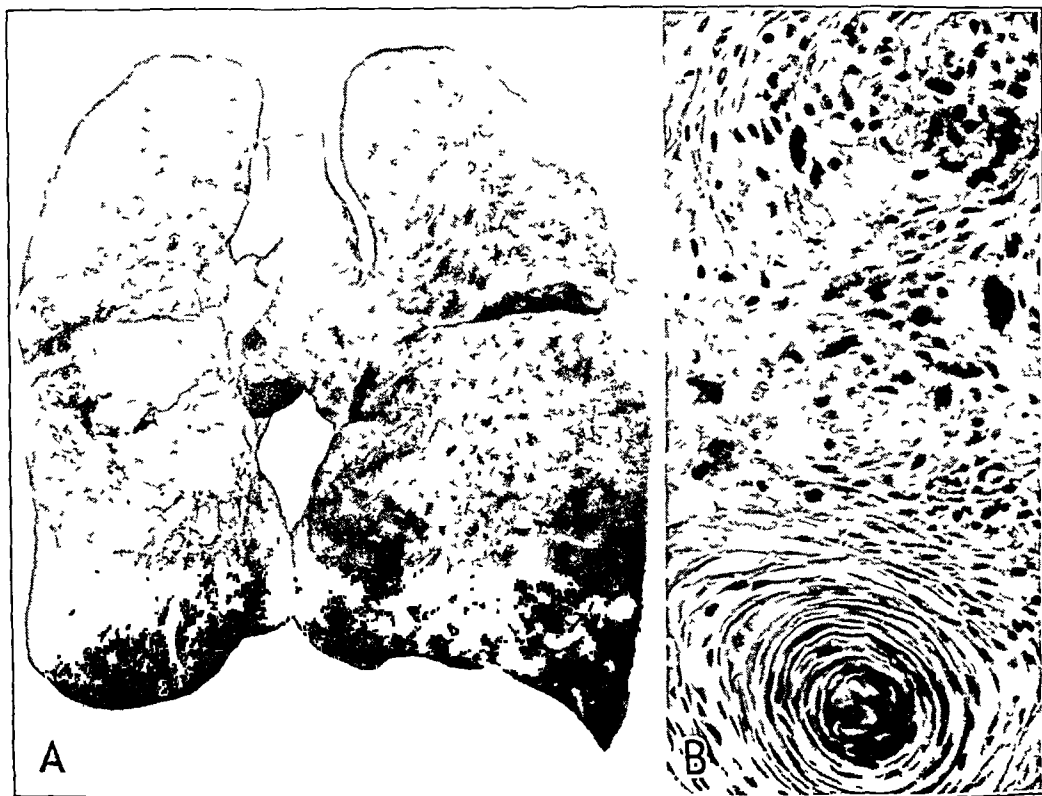


Fig. 9 (case 6)—*A*, photograph of gross specimen. *B*, photomicrograph showing a hyalinizing squamous cell cancer with epithelial pearls. No metastases were found anywhere. Hematoxylin and eosin stain;  $\times 330$ .

course was definitely and progressively downward. Clinically, it was obvious that a chronic, rather mild, fibroid tuberculosis on an old syphilitic infection had abruptly changed to a grave condition that became worse without remissions.

Autopsy was performed on July 12, 1931. In the midportion of the lower lobe of the left lung was a large caseous mass about 15 cm. across, rather sharply demarcated from the rest of the pulmonary tissue, with some sloughing in the central portion. There were old healed tuberculous nodules in both upper lobes, especially the right, and an acute pneumonic infiltration in the upper left and lower right lobes.

On the convex surface of the upper portions of the temporal and parietal lobes of the brain there was an accumulation of considerable clear yellowish fluid. No

tubercles were found here or at the base of the brain. There was no accumulation of fluid at the base, and no tumors were present on section.

The microscopic diagnosis was a typical squamous cell cancer.

*Comment.*—This case is similar to case 4 in that a cancer developed on a tuberculous infection. It is different in that no sign of metastasis was found anywhere. The tumor mass contained large numbers of tubercle bacilli; so many that after an acid-fast stain of a smear of the tissue the process was called caseous pneumonia. There was great surprise when the section was examined. Here was an example of a relatively easy clinical and roentgenologic diagnosis, with a confusion of the gross pathologic lesions.

CASE 7.—S. L., a Polish-American housewife, aged about 47, presented an uneventful early history. The onset of her condition was pleuritic pain in the lower right part of the chest ten months before death, fever, night sweats, cough expectoration, weakness, anorexia, insomnia, headaches and loss of weight. She went to the Cook County Tuberculosis Hospital for six months, where some improvement was noted, but this soon disappeared and she was readmitted with exaggerated symptoms and a marked dyspnea. This time she was sent to the sanatorium.

Physical examination by Dr. Fremmel revealed a malnourished woman with dyspnea and cyanosis, a lagging in the right side and increased tactile fremitus on the right. There was marked mental dulness. There was dulness over the upper part of the left lung with flatness over the whole right lung. Râles were heard on the right with amphoric breathing in the upper part and whispered pectoriloquy. On the left there were a few râles.

A roentgenogram revealed a dense shadow over the whole right lung, with a moderately dense shadow out from the left hilus, which was considered characteristic of tuberculous empyema. There was a resemblance to a malignant condition, but from the history it was considered more probably tuberculosis.

The important features of the laboratory examination were 4 plus positive Wassermann and Kahn reactions, sputum negative for tubercle bacilli, a profound leukocytosis (31,200 white blood cells) and an increased red cell count and hemoglobin (5,570,000 red blood cells and 95 per cent hemoglobin). An examination of a small quantity of a bloody pleural fluid revealed a "few monocytes and many varying sizes of lymphocytes." Some of the latter cells may have been tumor cells. A bronchoscopic examination was recommended, but it was not done.

Autopsy was performed on Sept. 6, 1931. The whole right lung consisted of a consolidated mass resembling caseous pneumonia. The upper lobe contained coal pigment and a slight amount of fibrosis. There was a metastatic focus in the midportion of the left lung resembling tuberculous bronchopneumonia. There were also discrete nodules toward the base and apex resembling foci of tuberculosis, with the difference that they had a circular rather than nodose appearance. The hilar lymph nodes contained some type of metastatic material. There were metastases only in the tracheal lymph nodes. The brain was not removed, by special request, although there were symptoms of a tumor of the brain.

The cytologic diagnosis was an "alveolar cell" cancer.

*Comment.*—This case presents the classic picture of so-called alveolar carcinoma of the lung. The gross pathologic process resembled the

gray stage of lobar pneumonia. The cells resembled normal alveolar cells, and without close observation might have been mistaken for large lymphocytes. That is what happened in the examination of the fluid from the pleura. No mitotic figures were found even on section. The patient's course was typical of tuberculosis, except that tubercle bacilli were never found and there was never a typical tuberculous empyema.

CASE 8.—J. R., aged 50, a Bohemian butcher, was from the private practice of one of us (A. J. H.). The patient's mother died of tuberculosis when the patient was 12 years old. His history was otherwise unimportant. The onset of his condition was with a cold and a cough nine months before death; then followed pleurisy with effusion seven months before death; severe cough with hemorrhage; the presence of blood varying from streaks to clots five months before death;



Fig. 10 (case 8).—Roentgenograms showing in *A* obliteration of all markings on the right and in *B* the stoppage of iodized oil in the right main bronchus.

gradually increasing dyspnea; epigastric pain; loss of weight; night sweats, and weakness. The patient was admitted to the sanatorium for complete study.

Physical examination by Dr. Collins showed the following signs and symptoms: There was no movement of the right side. The veins of the neck were dilated. Flatness existed over the right lung, and the left was normal. Bronchial breathing was heard over the upper anterior and posterior portion of the right lung; no râles were heard, but there were diminished breath sounds at the base of the right lung. The liver was enlarged. The diagnosis was "carcinoma or tuberculous empyema."

The roentgenogram revealed an opaque right side from the apex to the base. The left side was clear, probably owing to an empyema. After an injection of iodized oil, the right bronchus showed a complete stricture about 8 cm. from the bifurcation. Oblique and heavily exposed films revealed a few calcified lymph nodes near the hilus, but no other difference.

Paracentesis revealed a scant bloody fluid that clotted and was negative for tubercle bacilli and tumor cells.

Bronchoscopy revealed a mass in the right bronchus, obliterating the bifurcation, and granulated masses in the trachea, from which a specimen was taken that was found to be malignant.

Laboratory examination showed the pleural fluid and sputum to be always negative for tubercle bacilli. No cancer cells were found in the bloody effusion obtained by tapping the pleural cavity late in the course of the disease. An amyloid test was done, and 33 per cent of dye was removed in one hour. A biopsy specimen disclosed a medullary carcinoma of the small round undifferentiated cell type.

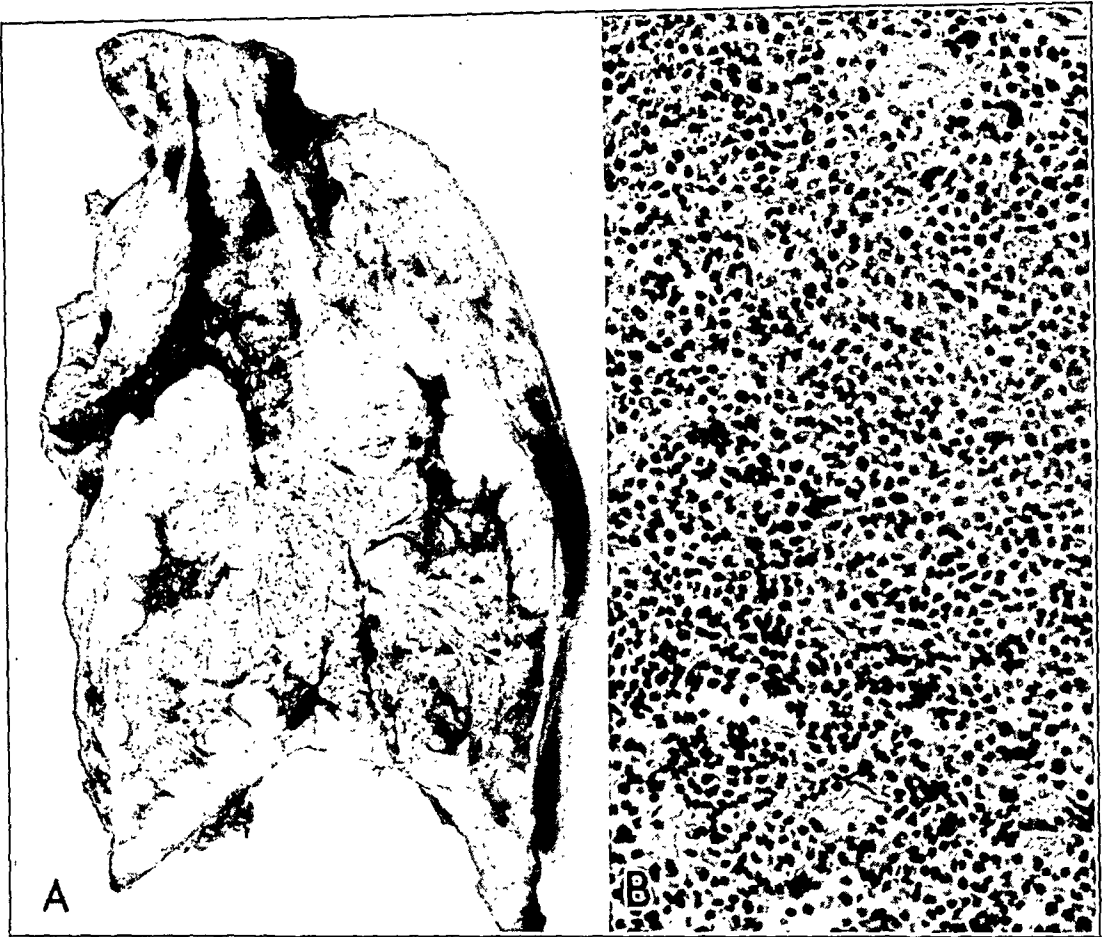


Fig. 11 (case 8).—*A*, photograph of the gross specimen. Note the bronchiectasis toward the base. *B*, photomicrograph showing a homogeneous type of undifferentiated small round cell. Hematoxylin and eosin stain;  $\times 330$ .

In the subsequent course the patient failed rapidly, breathing became stertorous, and death occurred only a few days after the bronchoscopy.

An autopsy was performed on Feb. 21, 1932. The right lung was solidified in its lower two thirds. The upper third was boggy and atelectatic. When the trachea and bronchi were opened the mucosae were found to be hemorrhagic. The right main bronchus showed nodules 2 cm. from the bifurcation. Farther down these increased, giving a corrugated effect. At the first division toward the origin of the bronchus of the upper lobe and extending radially to include the parenchyma of the lung, pleura and bronchial lymph glands was an irregular grayish-pink necrotic tumor mass. Many bronchi were seen to be dilated and to exude

mucopus from the cavities thus formed. The pleura was extensively infiltrated by a coat of tumor tissue from 2 to 3 cm. in depth. The bronchial lymph nodes reached a diameter of 8 cm. and contained a calcified focus and also what appeared to be a caseous tuberculous focus. The left lung was pinkish-gray-black. One fibrous adhesion extended to the thoracic wall from the apex, which contained a few small palpable nodules. There were metastases to the right pulmonary pleura, pericardium, bronchial periaortic and peripancreatic lymph nodes and liver.

*Comment.*—This patient presented early symptoms of tuberculosis, including a typical-appearing pleural fluid. The distinguishing feature was that no tubercle bacilli were ever found, although the effusions obtained in the first few tapplings were not examined, and many caseous and calcified lesions were present, indicating a very old and healed infection. Later, by injection of iodized oil and bronchoscopic section, the correct diagnosis was easily made. The one predominant cell was sarcomatous in appearance and perhaps would have been called that by the older pathologists. The metaplasia into the bronchial types of cell and structure, however, showed the true character.

CASE 9.—M. Z., aged 20, an Austrian office girl, who came to the United States two years before her death, did office work and then worked at a machine. At 4 years of age she had a gland removed from her neck; at 8 years of age she had diphtheria; at 14 and again at 16 she had influenza. After the first attack she was treated with tuberculin for a residual pain in her left side. After the second attack she noted an occasional fever. At 18 years of age she felt well again, but what was called appendicitis soon developed, for which an operation was performed. Pains developed in her chest after the operation, and she spit up a little blood. Ever since that time she had expectorated occasional blood-streaked sputum, but had no cough.

Physical findings by Dr. Caroline McDonald revealed a well nourished young woman apparently in good health, with a slight lagging on the right side, slightly impaired resonance in the upper part of the right lung, with more impairment posteriorly at the angle of the scapula, and a few râles. There was a large cystic mass in the region of the right ovary. The diagnosis was moderately advanced "A" tuberculosis, with a cyst in the ovary. Later there appeared a gradual consolidation of the whole right lung with nodules developing in the axilla and the cervical region. The right pupil became dilated also.

Roentgenologic examination showed a small tumor mass along the right main bronchus about 2 cm. in diameter, which was perhaps a lymph node. A later picture revealed a density of the whole right side, considered to be tuberculous empyema, abscess and tumor, at different times.

Laboratory examinations revealed the sputum to be persistently negative for tubercle bacilli, and the Wassermann reaction to be 2 plus, with other reactions practically normal. A biopsy of a subcutaneous nodule revealed carcinoma by frozen section.

Autopsy was performed on Aug. 29, 1924. The essential gross pathologic process was: a tumor mass in the right lower lobe about 7 cm. from the bifurcation. The mass was firmer than the surrounding tissue of the lung, which was collapsed, brownish, and contained scattering discrete nodules beneath the pleura and in the parenchyma. The hilar lymph nodes were enlarged into huge masses,

and they appeared to extend into the bronchus near the hilus in papillomatous masses. Metastases were found widely disseminated throughout the body as follows: large masses from 5 to 8 cm. in diameter in the liver, tracheobronchial lymph nodes, right and left pleura, kidneys, mesentery, pancreas, fundus of the uterus, glands of the hilus of the spleen, diaphragm, peritoneum, ovary and broad ligament, thyroid gland, right breast, Virchow's node (right) and gallbladder. The brain and cord were not removed. The right parovarium revealed a large sacculated tumor mass about the size of the fist, containing a large amount of serosanguineous fluid. There were accessory cysts along the tube and in the broad ligament. There were a few grapelike tumor masses around the left ovary and in the left broad ligament.

*Comment.*—The reasons for not considering the condition primary in the lung are: 1. There was a definite cancerous cyst of the ovary—a more common type of tumor in the female. 2. The cell type was the same as that found elsewhere. 3. The growth in the lung resembled primary cancer grossly but not microscopically. The cancer nodule pushed through the bronchus and elevated a normal bronchial mucosa with normal mucous glands. Cytologically, there was no pulmonary tissue that appeared cancerous.

It is possible that there was a double primary process, but it is difficult to prove and seemingly improbable.

CASE 10.—Mrs. G. N., an American housewife, aged about 44, was referred to Dr. Henrichsen by Dr. Brandle for diagnosis. No family history was obtained. The complaint was a cough for several months, without expectoration or blood. There was no loss of weight, and she felt well generally. She smoked heavily.

Physical findings by Dr. Henrichsen revealed increased breath sounds over the left anterior part of the chest, almost bronchial in character, with râles from the hilus up and outward on the left. With the history of cough and the tumor shown in the roentgenogram, a malignant condition was suspected, and the patient returned to Dr. Brandle.

A roentgenogram revealed a dense mass along the medial border of the left hilus that did not extend far into the pulmonary tissue. It resembled a mediastinal tumor.

The patient was operated on for an ovarian cyst, but did not recover from the operation.

Autopsy revealed a tumor mass completely enveloping the left main bronchus and measuring about 8 cm. across. The tumor mass had penetrated the main bronchus and had completely occluded it.

The cytologic diagnosis was an undifferentiated basal cell type of carcinoma.

*Comment.*—Owing to the operation for ovarian cyst, there is some doubt about the origin of the tumor in the lungs. The cell type, however, is characteristic of neoplastic pulmonary tissue. Without this definite proof, however, there could be no positive diagnosis of the origin. The history of being a heavy smoker may be of significance.

CASE 11.—G. I., aged 63, an American, with an uneventful early history, worked for forty-one years in a department store. Four years before his death an advanced

tuberculosis developed with cavities in both upper lobes. Eighteen months before death the patient had a nodule removed from the neck that proved to be a metastatic carcinoma.

According to the first roentgenologic report on the chest by Dr. Cook on May 14, 1929, the condition was "typical of well advanced tuberculosis." On Sept. 26, 1930, a fluid was noted on the left side. On Jan. 9, 1931, a phrenic exeresis was performed on the left side "with no frank evidence of metastatic malignancy," but on June 22, 1932, there were two well marked areas near the periphery that were "seen in metastatic conditions" and the right lung root showed "an active process which is probably of the same character."

The laboratory findings other than the biopsy revealed only a gradually progressing anemia and sputum negative for tubercle bacilli after March 21, 1930. Practically every common laboratory examination was performed, however.



Fig. 12 (case 11).—A photograph of a cross-section of the gross specimen, showing the tumor masses represented in the following roentgenograms. Note the primary tumor at the arrow and the point from which the section was taken.

Autopsy, performed on Sept. 4, 1932, revealed the following pertinent pathologic changes: A tumor crater was found in the right main bronchus measuring 2 cm. across and raised about 3 mm. above the surface of the mucosa. The base extended almost around the bronchus and up and down the bronchus for a distance of from 1 to 1.5 cm. After section, the tumor was found to penetrate through the wall of the bronchus as a solid white mass and extend outward into the tissue of the lung, involving lymph nodes, vessels and pulmonary structures for a distance of from 3 to 5 cm. The right pulmonary vein was penetrated by a fungating mass about 7 mm. across that proved to be tumor tissue, and was no doubt the source of the early metastases. There were two large grayish-white tumor masses in the bases of each upper lobe measuring about 10 cm. across, two in the apexes of each lower lobe measuring from 6 to 8 cm. in diameter, and several smaller ones in the apexes, middle lobe and bases of both lungs. The blood revealed the presence of tumor cells and mitotic figures. The hilar lymph nodes were markedly involved, as were the liver and the left submaxillary region including the skin.

The brain was not examined; however, there were no symptoms of involvement of the central nervous system (figs. 12, 13 and 14).

CASE 12.—J. D., aged 47, a German machinist, was a moderate user of alcohol and tobacco. He complained of cough that had been noted for four months, expectoration that had been present for one month, a transient pleuritic pain, dyspnea, fatigue, loss of weight and headaches. There had been one specimen of sputum positive for tubercle bacilli at the dispensary.



Fig. 13 (case 11).—*A*, roentgenogram taken thirty-nine months before death showing extensive tuberculosis more marked in the left lung. *B*, roentgenogram taken nineteen months before death showing marked healing of the tuberculosis with a suspicious thickening of the right main bronchus out from the hilus. *C*, roentgenogram taken eleven months before death showing an exaggeration of a tumor at the hilus with a large round mass appearing in the left upper lobe and a smaller one in the right lower. *D*, roentgenogram taken three months before death, showing an exaggeration of all the markings.

Physical examination by Dr. Davison revealed an impairment of motion and resonance at the apices of both lungs, more on the right; flatness and absence of



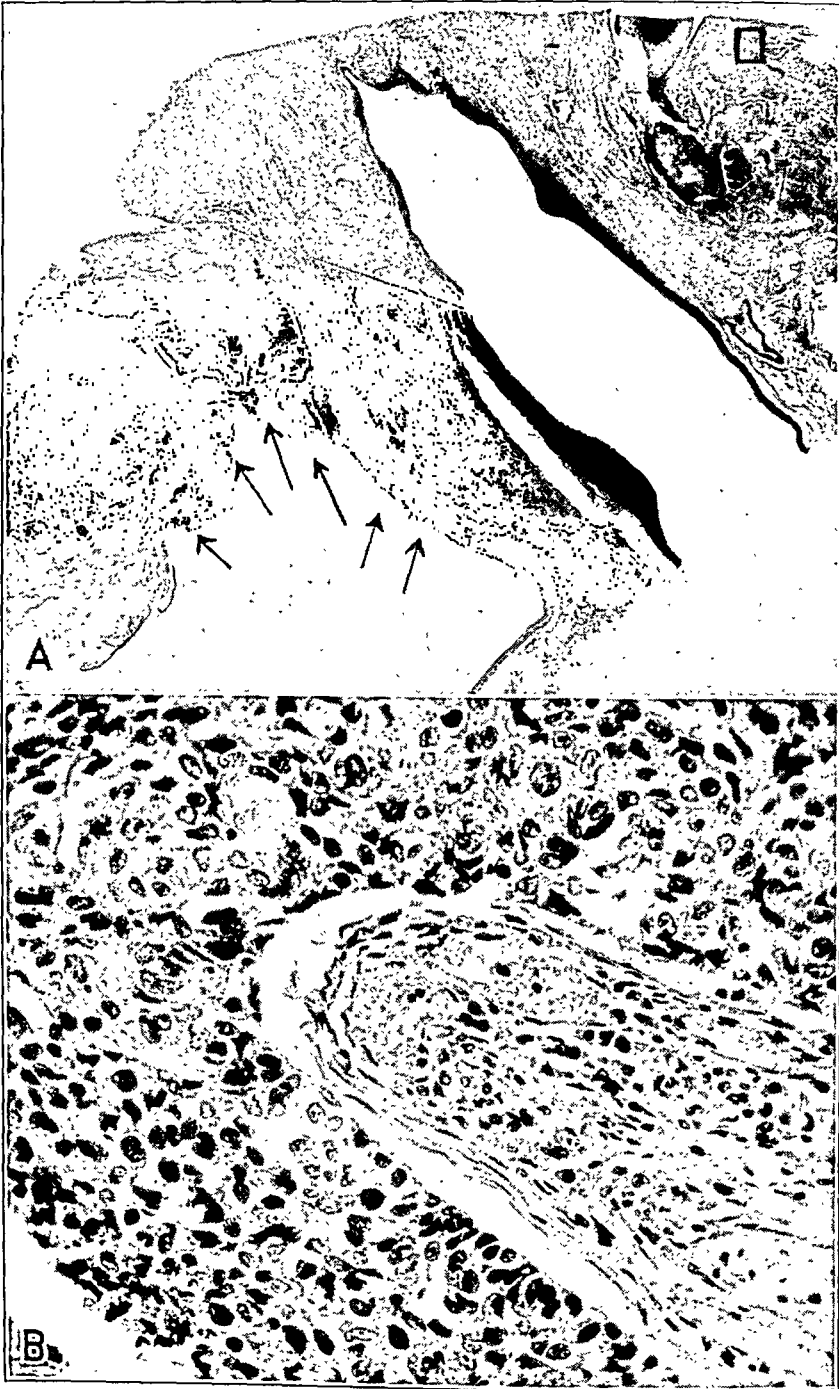


Fig. 14.—*A*, a conjoint photomicrograph of the bronchus (upper right corner) and the great vessels (lower). The primary tumor began in the bronchus (upper right) and extended around the pulmonary artery in the middle and into the pulmonary veins marked by the arrows. Hematoxylin and eosin stain;  $\times 6.6$ . *B*, an undifferentiated ("oat cell") type of nonhyalinizing squamous cell cancer, represented in small square in *A*. Hematoxylin and eosin stain;  $\times 330$ .

breath sounds at the base of the right lung; a few râles in the apex of the right lung. A malignant condition was suspected.

Roentgenologic examination by Dr. Cook showed that the findings were compatible with advanced pulmonary tuberculosis. Bronchoscopic examination revealed obstructions about 1.5 cm. from the bifurcation on the right but no tumor. A section of prepared pleural fluid revealed carcinoma cells. One examination for tubercle bacilli gave doubtful positive results. All other tests were essentially negative.

Autopsy, performed on Oct. 1, 1932, revealed a sclerous type of mesothelioma (endothelioma) of the right pleura, extending into the right lung, with other metastases to the liver and the left kidney. The brain was not examined, although the headaches were suggestive of metastases.

*Comment.*—A careful recheck of this specimen revealed a cancer of the small lower bronchi. Sometimes the differentiation of a so-called "endothelioma" from cancer of the lung is difficult.

CASE 13.—A. A., aged 52, a Pole, worked three years as a coal miner and then as a metal worker. Other factors were uneventful. The onset of his condition began with cough, expectoration and fatigue, eleven months before death. Subsequent symptoms were loss of weight, fever, night sweats, dyspnea and numbness in the left leg.

Physical examination by Dr. Davison revealed the base of the left lung retracted posteriorly; fremitus increased in the apexes but decreased in the base of the left lung; resonance decreased in the apexes and base of the left lung but increased elsewhere, and absence of breath sounds in the base of the left lung. The diagnosis was deferred. The roentgenologic examination at first was suggestive of a malignant growth. Iodized oil failed to reveal anything definite. There appeared to be metastatic tumors in the leg and the skull. A nodule from beneath the skin revealed a metastatic carcinoma. A pathologic fracture of the left leg occurred two months before death. Bronchoscopy was not completed because of noncooperation of the patient.

Autopsy was performed on Dec. 18, 1932, and revealed the following important pathologic changes: The lungs were markedly anthracotic as well as the pulmonary and hilar lymph nodes. The right apex contained an old fibroid tuberculous lesion with calcification. There was a fungating tumor at the base of the left main bronchus centering 5 cm. below the bifurcation and extending upward to the bifurcation and downward for another 5 cm. and into all adjacent bronchi. There was extreme bronchiectasis with numerous bronchiectatic abscesses. The tumor had grown forward and enveloped the great pulmonary vessels, completely occluding the upper main pulmonary vein and growing into it toward the heart and into the auricle in the form of a pendulous mass. There were numerous bronchiectatic cavities in the anterior part of both lobes, most of which contained encysted mucus. Microscopic examination revealed an undifferentiated basal cell carcinoma.

*Comment.*—The important feature here is the same as in case 11, the origin of the metastases by extension into the pulmonary vein. It appears that this may be the chief explanation of widespread metastases of cancers of the lung (fig. 15). This condition will no doubt be found more often if it is looked for.

## GENERAL ANALYSIS

In the analysis, only 12 of the 13 cases are considered because one was most likely metastatic and only simulated a primary carcinoma. It was included, however, because it resembled a primary carcinoma so closely.

The average age of the patients in this group of cases was 49.4 years for the males, 45.5 years for the females, and 48.7 years for both sexes; i. e., the incidence of cancer of the lung is chiefly in the fifth and sixth decades of life. There were 10 males and 2 females—a ratio



FIG. 15 (case 13).—Photographs of lung sections. *A*, posterior view showing the tumor in the left main bronchus and an apical fibroid tuberculous lesion in the right, found only at autopsy. *B*, anterior view showing a pendulous tumor growth extending into the left auricle from the left pulmonary vein.

of 5:1. The racial incidence is about what could be expected, that is, in proportion to the numbers of the various races represented. There were 3 Teutonic, 5 Slavic, 1 Celtic and 3 American patients. No history of carcinoma was obtained from any patient. The occupational incidence was of the same degree and significance as the racial incidence. There were 1 clerk, 2 housewives, 6 inside laborers (1 waiter, 1 mechanic, 1 baker, 1 barber, 1 tailor and 1 butcher) and 3 outside laborers (1 brick truckman, 1 coal miner and 1 motorman). Of disease inci-

dence, it is noteworthy that 4 patients gave a history of influenza; in 2 patients, this immediately preceded the onset if it was not actually the onset, simulating influenza. In several of Hunt's cases the condition began with influenza. One patient's condition began with a "cold"; another patient gave the history of a chronic bronchitis; 1 had healed minimal tuberculosis; 2 had chronic moderately advanced tuberculosis, and 1 had healing advanced tuberculosis. One positive finding was doubtful. Two patients had 4 plus Wassermann reactions, and 3 gave histories of excessive smoking. One patient (case 6) had a 4 plus Wassermann reaction and tuberculosis.

The appearance of symptoms may be summarized much as in previous paragraphs. Cough led the list (first, 8 times; second, once); pain came next, appearing first in 2 cases, second in 4 and third in 1; the other symptoms appeared later, the most important of which was dyspnea. In 1 case the first symptoms were not detected because of tuberculosis; in another, because of influenza. Tubercle bacilli were found in 5 cases. In 1 case the presence of bacilli confused the issue and caused a correct clinical diagnosis to be reversed, and in another a tuberculous lesion was discovered only at autopsy. In the other cases the finding of tubercle bacilli made little difference. One patient with a 4 plus Wassermann reaction gave a history of an old syphilitic infection, but another patient (a woman) with this reaction gave no history of syphilis.

In the physical findings, the presence of lagging and of limitation of motion were sufficiently important to cause the examiner to lay special emphasis on them. They were recorded four and five times, respectively. A flat chest was emphasized in 3 cases. Distended veins in the neck (a late sign) were present in 2 cases. The most important physical signs were those of tumor, impaired resonance, dullness and flatness over the tumor and hyperresonance above. Impaired resonance is not so important, because it may be present in any pathologic process in the lung; flatness is not so important either, because it nearly always appears late in the disease, and when it does, the diagnosis is obvious. A sharply outlined area of dullness, however, is set apart rather early as something unusual. This is particularly true in the lower two thirds of the chest. In 7 of the patients, dullness was found rather early. The signs of obstruction were manifested by diminished breathing beyond the tumor, with rough or bronchial breathing in the region of the tumor. Râles were usually few and of a moist type. Occasionally they were absent until late in the disease. The symptoms and findings of metastases were variable, depending on the location. In the spine there was frequently a compression myelitis, and in the brain, signs of brain tumor.

The diagnosis was made by autopsy in all 12 cases. Clinically, a definite diagnosis was made in 5 cases, a presumptive diagnosis in 5 and an incorrect diagnosis in 2. Roentgenologically, definite evidence was found in 6 cases (in 2, only by the spinal metastases), presumptive evidence in 3 and negative evidence in 3. Bronchoscopy and biopsy established the diagnosis in 2 cases, but gave negative results in 1, while biopsy of a metastatic growth established the diagnosis in 3. In 1 of these (case 11) the first sign of cancer was from a metastatic growth in the submaxillary region. The advanced tuberculosis confused both symptoms and physical findings until the pulmonary metastases appeared in the roentgenograms. The laboratory examinations (exclusive of the study of sections) did not contribute any positive information that was of help in diagnosis, except in case 12 in which the diagnosis of a malignant growth was made on the basis of the sectioned sediment of the pleural fluid. With our present information and equipment, there is only 1 of the cases in which there would be any excuse for missing the diagnosis either clinically or roentgenologically, and in all but 2 or 3 the diagnosis should have been made by bronchoscopy and biopsy. The "alveolar" type (case 7) was similar to tuberculosis, especially early. Three of the patients with sputum positive for tubercle bacilli presented other symptoms so characteristic of cancer that there should have been little difficulty in discounting the tuberculous findings.

We feel that laboratory examination can aid a great deal more than it has in the past. The sputum and fluids of any kind should be centrifugated, the sediment hardened in formaldehyde, sectioned, stained, and the sections studied carefully. In 1 patient (case 7, the "alveolar" type) numerous cells were found in the pleural fluid and sputum, but there were no mitotic figures; furthermore, the cells resembled large lymphocytes so closely that they were thought to be modified lymphocytes. Since this report was finished, a definite diagnosis has been made in 2 cases by means of sectioned sputum before any other method was employed.

#### COMMENT

Since a tremendous and unquestionable increase in cancer of the lung has been revealed by a study of the records of autopsies, it is pertinent to attempt to analyze the causes. While disease, smoke, dust and modes of living may have been the cause of some of the increase, we feel that better diagnosis and changed conditions have contributed the most.

Significant features from the statistical figures are that at the beginning of each report the incidence is nearly always low, irrespective of the time, which may be 1900 with some authors or 1915 with others.

Following the World War all figures rise rather sharply till many exceed 2 per cent of all autopsies, reaching the peak about 1928. This again raises the question of whether all the patients with cancers of the lung were found or whether those who came into the clinics may not have been a sporadic selection. At least this must be considered, because Lubarsch's<sup>70</sup> figures for 1920 revealed an incidence at autopsies of only 5 per cent for all Germany. Karsner<sup>71</sup> estimated the incidence at autopsies for America at 0.7 per cent. With over 95 per cent of bodies not examined, it behooves one to be cautious in drawing conclusions from work done on the remainder, no matter how carefully done. As it is, all reports are not acceptable when judged by the requirements proposed by Weller, which include an autopsy with complete microscopic study and the elimination of all possibilities of metastasis. For instance, Duguid,<sup>32</sup> who wisely speaks of "primary intrathoracic neoplasms," was able to confirm only 78 of 195 diagnoses by microscopic examination.

Furthermore, certain hospitals and clinics have types of patients who tend to contribute more cases of cancer of the lung than others. This holds where there are low percentages of women and children, because the disease is more prevalent in men past middle life. In our hospital, for example, we have a rate of 2 per cent according to the statistics of autopsies (greater, in fact, than that of general cancer), but it must be noted that we have obtained nearly 100 per cent necropsies in cases in which death occurred from cancer, but only 35 per cent in all cases in which death occurred. This gives a rate of about 0.6 per cent of all deaths instead of 2 per cent. Obviously, our figures for general cancer are not high and will give no information of value. Duguid mentioned the unreliability of statistics from teaching institutions, where great zeal is shown in securing the unusual type of case for teaching purposes.

The percentage of cancers of the lung, therefore, may depend largely on what happens in that unknown group of patients not now coming to autopsy, and until we have complete data on that group we must consider the increase only "apparent."

We have attempted to make a useful classification that would serve the purposes of diagnosis and treatment. Thus far therapeutic results have been poor. This is not due so much to the hopelessness of the situation as to diagnostic shortcomings. Recently several reports have shown that operative procedures are effective even when the lesions are advanced, owing mainly to the fact that many metastasize rather late.

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70. Lubarsch, O.: *Einiges zur Sterblichkeits-und Leichenöffnungsstatistik*, Med. Klin. **20**:299, 1924.

71. Karsner, H. T., and Saphir, O.: *Small Cell Carcinoma of the Lung*, Am. J. Path. **6**:559, 1930.

Harrington,<sup>72</sup> Jackson and his associates<sup>67</sup> and Allen and Smith<sup>73</sup> have given high hopes for favorable surgical effects.

We have rather arbitrarily divided the field into 7 groups, according to the effects produced directly or indirectly. The grouping is as follows:

1. An involvement of the basal layer of the bronchi or bronchioli, causing a cough; slight mucoid expectoration, sometimes blood-tinged, with symptoms only of mild bronchial irritation. There is slight, if any, shadow in the bronchus, and there are no definite physical signs. The diagnosis is established only by a bronchoscopic view or section.

2. Constriction of the lumen of the bronchus. The signs are dyspnea, shortness of breath and more cough than in the first group. There is a diminished breath sound on auscultation distal to the involved region. The shadow in the roentgenogram is definite but variable. The endoscopic view usually shows a fixed bronchus; the bronchoscopic section reveals the tumor if it is on the main bronchi.

3. Parenchymal extension. This is an exaggeration of the preceding process, with metastases into the parenchyma of the lung and regional lymph nodes.

4. Parenchymal extension, presenting signs of cavitation.

5. Pressure on adjacent structures, resulting in dysphagia, stridor, aphonia, irregular pupils and dilated veins in the neck, depending on the structures involved.

6. Pleural involvement with unrelenting pain of a variable character. A diffuse shadow is shown in the roentgenogram, usually due to effusion.

7. Metastases. They are variable, depending on the location, and are caused chiefly by an invasion of the tumor into a pulmonary vein. In metastasis to the central nervous system practically any nervous disease may be simulated.

This grouping may be simplified on the basis of therapeutic possibilities. Accordingly, we rearrange it into 3 groups according to the degree or types of surgical procedure:

1. Simple excision of the primary nodule by means of the bronchoscope, followed by the application of radium (includes most of the cases in group 1 in the foregoing classification).

2. Lobectomy (*a*) when the primary nodule cannot be reached by a bronchoscope (includes a few cases in group 1) or (*b*) when the

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72. Harrington, S. W.: *Surgical Treatment of Tumors of the Lung and Mediastinum*, Surg., Gynec. & Obst. **52**:417, 1931.

73. Allen, C. I., and Smith, F. J.: *Primary Carcinoma of the Lung*, Surg., Gynec. & Obst. **55**:151, 1932.

condition is more advanced (includes cases in group 2) when the metastases have been only by direct extension (case 6) or locally by way of the lymphatics.

3. Palliative, if at all (includes groups 3 to 7, inclusive).

One is struck by the resemblance of this last grouping to the old classification of tuberculosis into early, moderate and far advanced groups.

#### SUMMARY

An epidemiologic and clinical study has been made of primary cancer of the lung, with reports of 13 cases, 12 of which were unquestionably primary in the lungs and bronchi and 1 primary in the ovary. There has been an approximately tenfold increase in the number of cases of cancer of the lung coming to autopsy within the last forty years, and a twofold increase in the last ten years. There is no valid evidence, however, to prove an increase in the general incidence of the disease except where there is contact with radioactive dust (Schneeberg and Joachimstal miners). The increase that has occurred may be partly accounted for on the basis of (1) the increased life expectancy from 43 to 58 years in approximately the last half century; (2) a better knowledge of the causes of other pulmonary diseases (e. g., the knowledge resulting from the discovery of the tubercle bacillus); (3) better diagnostic equipment (x-ray apparatus, bronchoscope and similar equipment); (4) increased zeal on the part of the medical profession and laity (better hospitalization, better transportation and other factors); (5) a changed attitude on the part of the pathologists in recognizing as primary carcinomas tumors that were once called metastases and sarcomas. It is not justifiable, therefore, to claim an increase in cancer of the lung until all the unknown factors are studied (such as the relative number of cancers of the lung that occur in rural districts).

The symptoms and clinical findings are reviewed, as well as the diagnosis and the differential diagnosis. For a diagnosis, reliance should be placed on a gradually appearing cough (commonly in men past middle life), followed by a variable but constant pain, and expectoration of sputum frequently streaked with blood, all of which may be accompanied with or followed by dyspnea. Other less common signs are anorexia, fever, loss of weight, symptoms due to pressure (dysphagia and aphonia) and a variety of symptoms due to metastases. The physical signs reveal the presence of a gradually increasing bronchial tumor, with limitation of motion of the affected side, slight or no moisture at first, decreased breath sounds distal to the bronchial obstruction, hyperresonance above, dullness, and ultimately flatness over the tumor. The roentgenogram reveals a gradually progressing growth of tumor out from the hilus or along a bronchus, and the growth may be



diffuse or circumscribed. The endoscopic view reveals a "woody" or fixed bronchus, and study of a bronchoscopic section generally clinches the diagnosis.

The laboratory examination should first reveal a scant or mucoid sputum, sometimes streaked with blood or tinted with hemoglobin, free from tubercle bacilli. Later, tumor cells should be found in the sputum or pleural fluid. Such early findings offer the only opportunity for permanent therapeutic aid.

A pertinent observation has been recorded pertaining to distant metastases from cancer of the lung. They seem to depend on the rapidity and extent of the growth of the primary tumor into a pulmonary vein.

A practical classification is given according to the various stages of the disease and also from the standpoint of diagnosis and therapeutic possibilities.

# DIFFUSE ULCERATION OF THE ESOPHAGUS AND TRACHEA ASSOCIATED WITH DIABETES MELLITUS

ABSENCE OF ARTERIOSCLEROSIS

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Diffuse ulceration of the esophagus, of a degree sufficient to produce esophageal symptoms, is very unusual in the absence of obstruction. A lesion of this type was found in the first case that we report. We had not previously observed such diffuse ulceration except at necropsy, when in all probability postmortem changes were at least partly responsible. Similarly, we had not observed diffuse ulcerative tracheitis, as in the second case. That both of these uncommon lesions occurred in persons with diabetes suggests an etiologic factor in the metabolic abnormality. That patients with uncontrolled diabetes have a predilection for infectious diseases is attested by general experience, but, so far as we have learned, the complications considered here have not been reported in the literature on diabetes.

## REPORT OF CASES

CASE 1.—*Lesion of the Esophagus.*—A farm laborer, 24 years of age, manifested abruptly the cardinal symptoms of diabetes. Two weeks later, in November, 1924, he was admitted to the hospital, and urinalysis disclosed the presence of large amounts of sugar. The sugar content of the blood was 210 mg. per hundred cubic centimeters. The patient was 68 inches (173 cm.) tall, and weighed 145 pounds (65 Kg.). There was no family history of diabetes or of any other abnormalities of metabolism. The patient had appendicitis at the age of 7 years, for which appendectomy was performed; diphtheria at 17; influenza with pneumonia at 19; a fracture of the jaw from the kick of a horse at 20; acute tonsillitis at 21, and bronchopneumonia at 23.

General examination revealed enlarged tonsils containing pus, slightly enlarged cervical lymph nodes, ichthyotic skin and a systolic murmur over the apex of the heart. The blood pressure in millimeters of mercury was 92 systolic and 64 diastolic. The determination of the basal metabolic rate was +3 per cent. The patient was instructed to observe dietary restrictions and to use insulin. When he was dismissed from the hospital, the urine was free from sugar, and he was receiving 10 units of insulin daily and a diet of 52 Gm. of carbohydrate, 44 Gm. of protein and 218 Gm. of fat. Tonsillectomy was advised.

The patient did not follow dietary instructions accurately. His wife deserted him, and his family objected to his living with them. He was in poor economic

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circumstances, and lived alone, largely supported by charity. In April, 1925, a physician was called who found him in a "hysterical convulsion." The urine contained sugar; the temperature was 100 F., and the throat was inflamed. There was an odor of whisky in the room. Arrangements to place the patient in an institution for the indigent could not be made.

Three months later, in July, 1925, the patient was brought to the Mayo Clinic and was admitted to the hospital in a state of diabetic acidosis; he was stuporous and complained of abdominal pains; his skin and tongue were dry; he was hyperpneic, and the odor of acetone was strong. The carbon dioxide-combining power of the blood plasma was 10 per cent by volume; the concentration of sugar was 415 mg., and that of urea was 60 mg., per hundred cubic centimeters of blood. This episode had been initiated by the patient's inability to secure the proper diet and by his neglecting to take the regular doses of insulin. The usual measures to combat coma proved effective, and four days later the patient was dismissed from the hospital with instructions to attend an outpatient class for diabetic patients. His attendance was irregular, and at no time was the glycosuria satisfactorily controlled. He did, however, continue to take insulin in doses of from 30 to 50 units daily, and was thereby able to maintain his weight and reasonable strength, and to avoid coma. He remarried, and became the father of an infant in whom diabetes developed at the age of 1 year and 10 weeks. In April, 1929, the patient was apprehended for larceny and was committed to the state penitentiary. The prison attendants are reported to have said that they would "break him of the insulin habit." Three or four attacks of coma occurred when he was in the penitentiary. Three and a half months later, when discharged on parole, he weighed only 100 pounds (45 Kg.), having lost 60 pounds (27 Kg.). During the last few weeks in the penitentiary pain on swallowing appeared in the substernal region; sometimes it was so severe that he could not eat. Solid food had to be washed down with water. The pain was burning, and extended from the sternal notch to the epigastrium. Twice he had vomited blood-stained material. Roentgenograms of the stomach and esophagus did not reveal abnormalities, but on esophagoscopic examination an extensive annular ulceration was seen in the lower half of the esophagus with little, if any, reduction in the lumen of the esophagus. This area was covered with a necrotic membrane and bled easily. The serologic reaction for syphilis had never been positive, and was negative on this examination.

Severe chronic acidosis existed when the patient left the penitentiary, but this was brought under control, and rapid gain in weight and strength followed. The ulceration in the esophagus was treated by the application of a solution of 20 per cent silver nitrate, and by August, 1930, on direct examination, the mucous membrane seemed to be much improved; however, ulceration was still present. The blood pressure on July 21, 1930, was 124 systolic and 90 diastolic.

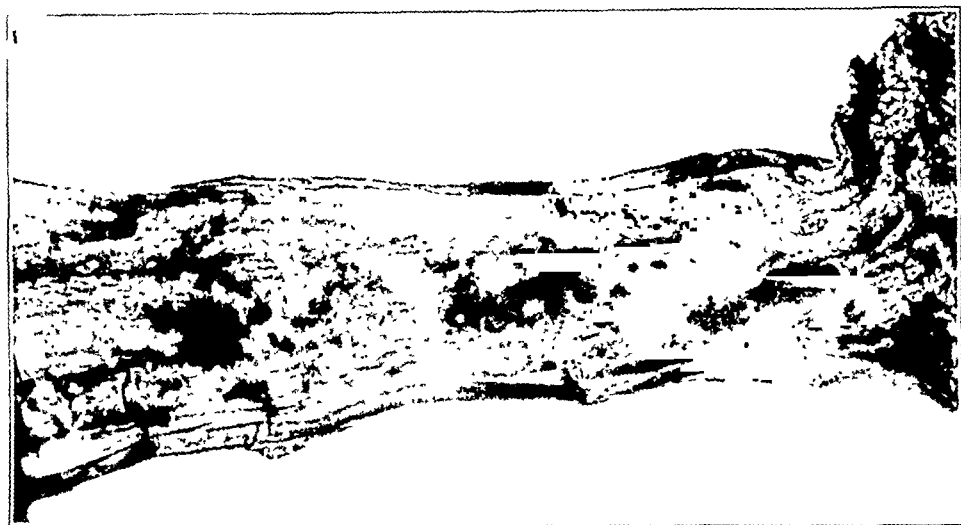
Some time after this, the patient escaped from the surveillance of the police, and in January, 1931, we were informed by a physician of his death in another state from diabetic acidosis. The patient had been in coma for three days. The body was returned to Rochester, Minn., where necropsy was performed. The anatomic findings were diabetes mellitus (clinical) with diabetic coma (clinical), atrophy of the pancreas, bilateral bronchopneumonia and subacute ulcerative esophagitis. The pancreas weighed 32 Gm. and appeared normal, except that it was small (the normal weight is 75 Gm.). The aorta was no more sclerotic than would be expected for a normal person of this man's age. There were a few streaks and patches of fatty infiltration such as we classify as arteriosclerosis, graded 1, but which some observers would not designate as arteriosclerosis.

In the esophagus were numerous superficial areas of ulceration which were more prominent in the lower third; its wall was considerably thickened throughout (see illustration). The stomach and duodenum appeared normal.

Microscopic examination of the pancreas disclosed a slight increase in the connective tissue. The acinar elements, however, including the islands, appeared normal, although the islands seemed fewer than usual. The aortic arch was not abnormal. The intima was unbroken. The vasa vasorum appeared normal.

**CASE 2.—Diffuse Ulcerative Lesion in the Trachea.**—A salesman, aged 57, came to the clinic in June, 1930, because of hoarseness. For seven months he had noticed hoarseness when singing, and for three months, when speaking. For three years, since the extraction of a few teeth, his weight had fallen from 172 to 167 pounds (78 to 75 Kg.). He had diphtheria at the age of 13 years and influenza at the age of 45.

The first twelve-hour specimen of urine was found to contain 30 Gm. of sugar, but no acetone bodies. On first examination, the blood sugar was found to be



Diffuse ulceration of the esophagus associated with diabetes mellitus in the absence of arteriosclerosis.

272 mg. per hundred cubic centimeters with the patient fasting. A diagnosis of diabetes mellitus was made. The serologic test for syphilis gave negative results. Indirect examination of the larynx revealed thickening in the subglottic area, with ulceration and crusting that extended into the trachea. On bronchoscopic examination, a similar condition was found to involve the entire trachea. The ulceration was strikingly similar to that seen in the esophagus of the first patient. It may be noted that there was no history of diabetes or other metabolic disease in the patient's family.

The patient was admitted to the hospital. The diabetes responded promptly to dietary treatment and insulin. A solution of potassium iodide was given by mouth, and the larynx and trachea were treated daily with a spray of mineral oil. When the patient was dismissed, twelve days later, the urine was free from sugar, and the sugar in the blood was 100 Gm. per hundred cubic centimeters, with an intake of food consisting of 73 Gm. of carbohydrate, 53 Gm. of protein and 197 Gm. of fat, and an insulin dosage of 10 units daily. Subsequent reports indicated gradual improvement of the ulcerated trachea.

## COMMENT

These cases of diabetes are reported mainly because of the discovery of unusual and, so far as we know, previously unrecognized complications—diffuse ulceration of the esophagus in the absence of any obstructive lesion and a similar ulceration of the trachea. The possibility of an etiologic relationship in the accompanying metabolic abnormality is considered. The first of these cases is also of interest because arteriosclerosis, other than a few patches and streaks of fatty deposits in the intima that would be expected in any man of the patient's age, could not be found at death. Weichselbaum<sup>1</sup> and other investigators have suggested that arteriosclerosis may be the cause of diabetes in many cases in which the two conditions are found accompanying each other, and not, as is usually assumed, the result of diabetes. This case adds strength to such a view. The diabetes was severe; it persisted, with ineffectual efforts at control, for six years; periods of severe acidosis occurred frequently. Under these circumstances, the lipids of the blood must have been abnormally high most of the time, yet arteriosclerosis did not develop to a degree that can be considered abnormal.

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1. Weichselbaum, A.: Ueber die Veränderungen des Pankreas bei Diabetes mellitus, Sitzungsab. d. k. Akad. d. Wissensch. Math.-Naturw. Kl. Wien **119**:73, 1910.

# HUMAN CAPILLARIES IN HEALTH AND IN DISEASE

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The capillaries constitute a most essential unit of the circulatory system,<sup>1</sup> the part about which least is known. Technical improvements have greatly facilitated capillary studies. The apparatus used for our studies was recently described in detail.<sup>2</sup>

## NORMAL CAPILLARIES OF THE SKIN

The first impression one gains in a study of the capillaries is that even when normal they are subject to a wide range of variation, not only in different persons, but within the same person. This is true of all anatomic parts. One must therefore guard against drawing conclusions from small differences in structure or in reaction.

*Appearance.*—It is known that the capillaries are the finest terminal connecting loops between the arterioles and the venules. Each capillary is divided into a narrow, constricted arterial limb and a wider, more dilated venous limb. The diameter of the arterial side may be less than the diameter of a red blood cell or large enough for several to pass through at once. In the living human being, with the use of reflected light, the walls of the capillaries are invisible, and only the column of blood cells is seen. This has often given rise to erroneous conclusions. Frequently, there is a break in the column of cells and serum alone passes through. The passage of these spaces along the loops has been described as peristaltic waves. This theory will be considered later. The capillary wall consists of an inner endothelial layer and an outer muscular layer. The muscular layer is not continuous, but consists of a widely meshed network of fine fibrils which connect with nucleated cells, first described by Rouget.<sup>3</sup> These cells and fibrils probably make

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1. Krogh, A.: *The Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1929.

2. Duryee, A. W., and Wright, I. S.: *Modern Methods for the Study of Human Capillaries*, *Am. J. M. Sc.* **5**:664 (May) 1933.

3. Rouget, C.: *Mémoire sur le développement de la technique contractile des vaisseaux*, *Compt. rend. Acad. d. sc.* **79**:559, 1873; *Sur la contractilité des capillaires sanguins*, *ibid.* **88**:916, 1879.

up the contractile system of the capillaries. There is evidence to show that there is a regulating mechanism controlling these systems, either by a minute connecting nerve fibril or by direct spread of nerve impulses. Vimtrup<sup>4</sup> claimed to have demonstrated Rouget cells in man, but Spalteholz<sup>5</sup> questioned that the nuclei seen by Vimtrup were those of true Rouget cells (Krogh<sup>1</sup>). The average number of these cells per millimeter of animal capillaries is from twenty to fifty. The total length of one cell with its fibrils averages about from 40 to 80 microns.

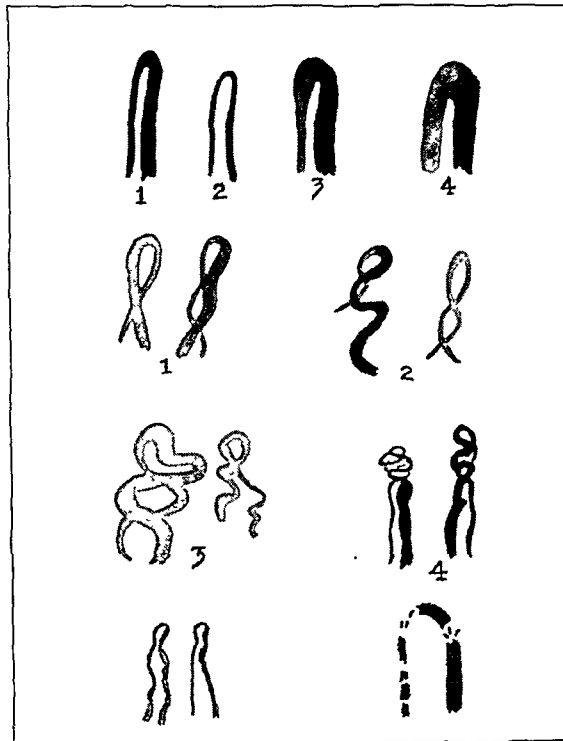


Fig. 1.—Schematic illustration portraying the common morphologic variations in capillaries of the human nail fold. The lowest line represents the “moth-eaten” capillaries in arteriosclerosis and a capillary with breaks in the column of cells which are filled with serum.

The normal thickness of the endothelium appears to be somewhat less than 1 micron (about 0.8 micron).

4. Vimtrup, B.: Beiträge zu Anatomie der Capillaren: I. Ueber contractile Elemente in der Gefasswand der Blutcapillaren, *Ztschr. f. d. ges. Anat.* **65**:150, 1922; II. Weiter Untersuchungen über contractile Elemente in der Gefasswand der Blutcapillaren, *ibid.* **68**:469, 1923.

5. Spalteholz, W., in Jadassohn, J.: *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1927, vol. 1, p. 379.

Heimberger<sup>6</sup> stated that the capillary loop in each papilla of the human nail fold is surrounded by a continuous lymph space traversed by a number of threads or septums which keep the loop in position.

He<sup>7</sup> also described short, very fine arteriovenous anastomoses connecting the peripheral arterioles and the venules, short-circuiting the capillaries and used under certain conditions subsequently described. Intracapillary anastomoses may more rarely be seen. These intracapillary anastomoses appear to have the power of going in and out of action independently of the rest of the capillary with which they are connected. This would be further evidence in favor of the presence

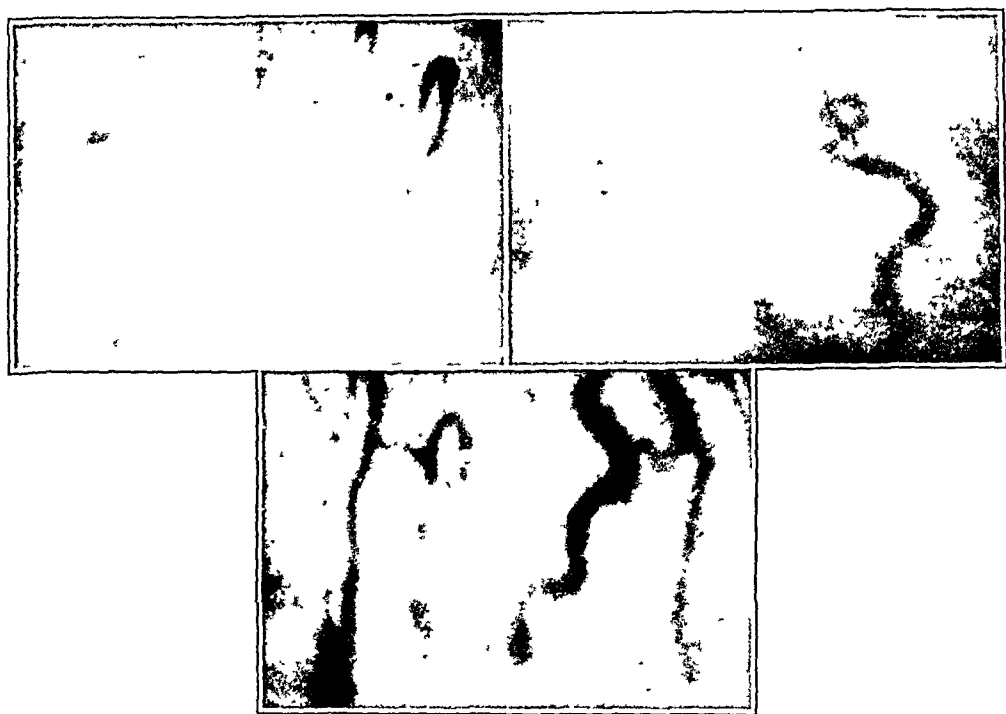


Fig. 2.—Photographs of intracapillary anastomoses. These can be accepted as proved only when cells have been observed to pass from the main capillary loops through these anastomoses. (These and all accompanying photographs are unretouched. They are enlargements made from 35 mm. film on which the magnification is  $\times 60$ .)

of Rouget cells or their counterpart as emphasized by one of us (Wright<sup>8</sup>).

6. Heimberger, H.: Beiträge zur Physiologie der menschlichen Capillaren: III, Verhalten auf Reizung mit galvanischem Strom, *Ztschr. f. d. ges. exper. Med.* **51**:112, 1926; Beiträge zur Physiologie der menschlichen Capillaren: V, Färbeversuche am Capillarendothel und die Lymphräume des Papillarkörpergewebes, *ibid.* **55**:17, 1927.

7. Heimberger, H.: Beiträge zur Physiologie der menschlichen Capillaren, *Ztschr. f. d. ges. exper. Med.* **46**:519, 1925.

8. Wright, I. S.: Intra-Capillary Anastomoses, *J. Clin. Investigation* **2**:835 (July) 1932.



The venules and arterioles do not subdivide into capillaries in a uniform manner. In some nail folds the arteriole and the venule can be seen running parallel to the edge of the nail fold with the arteriolar loop of the capillaries branching off at right angles to the arteriole and the venous portion of the capillary loop emptying at approximately right angles into the venule (fig. 3 *A*). We have observed, less commonly, variations from this type in which the arteriolar limb received its blood supply from arterioles which approached in an irregular manner and were indistinctly seen, and the venous portion of the capillary loops emptied into a venule which appeared like the trunk of a tree with several venules emptying into it at different levels and which in its turn emptied into a large venous channel at a deeper level (fig. 3 *B*). Many variations from these common types may be seen.

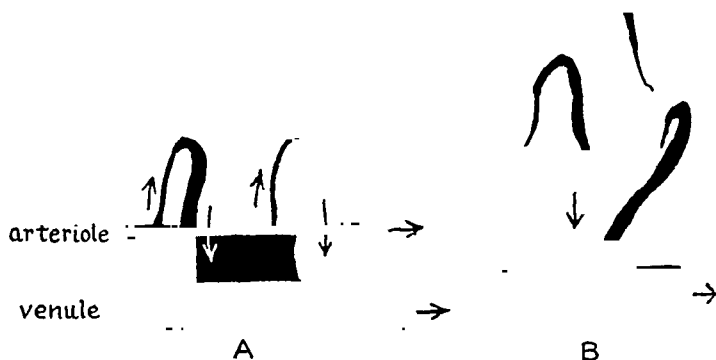


Fig. 3.—Types of arteriole-capillary-venule patterns.

Hagen<sup>9</sup> called attention to a constriction of the capillaries associated with the aneurysmal bulging and a tendency to bleed at the time of the menses. He also suggested changes with the seasons. These claims need much more confirmation.

*Age.*—The appearance of the capillaries changes with increased age. In new-born infants there is seen a network of capillary tubes which do not definitely appear as loops. With normal development to adulthood, loops gradually appear. These elongate slowly and tend to become somewhat more tortuous as senescence approaches. As will be discussed later, certain pathologic conditions greatly accentuate this. Most adults have scattered, very tortuous loops. These become significant as they increase in number, until in certain conditions described later, practically all of the capillaries are tortuous.

9. Hagen, W.: Die Schwankungen im Capillarkreislauf, *Ztschr. f. d. ges. exper. Med.* **14**:364, 1921; Periodische, konstitutionelle und pathologische Schwankungen im Verhalten der Blutcapillaren, *Virchows Arch. f. path. Anat.* **239**:504, 1922; *Deutsche med. Wchnschr.* **48**:1507 (Nov. 10) 1922.

Cutter and Marquardt<sup>10</sup> showed by means of a negative pressure-producing apparatus that fragility of the capillary walls increases in direct proportion to the age.

*Actual Size.*—If a capillary is of sufficient diameter to permit the passage of two or more red blood cells at the same time, a definite axial stream is established with a surrounding zone of plasma. As the capillary walls are invisible, it is then difficult to determine the exact size of the capillary in question, although the apparent shape, as shown by the blood stream, remains recognizable under practically all conditions. The large white corpuscles can readily be seen as they come

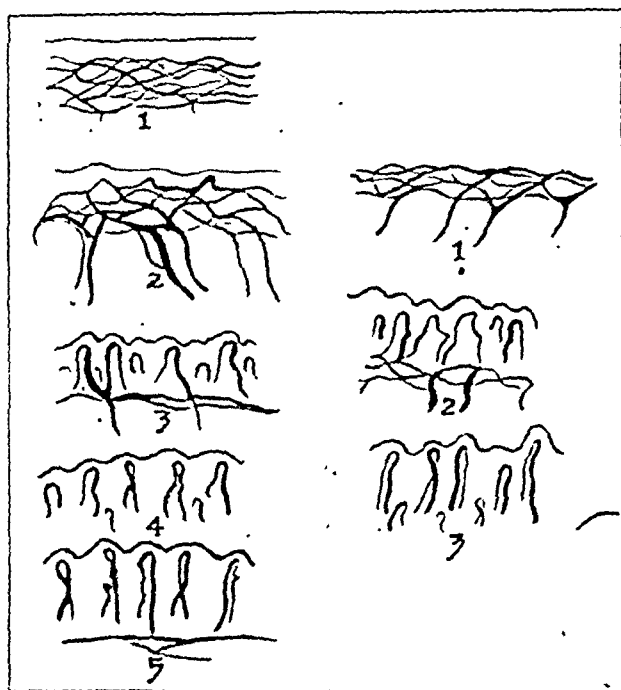


Fig. 4.—Schematic drawings of the development of capillaries in man. Number 1 in each case represents the capillary network in the new-born infant, and the successive sketches show the development to normal adulthood.

along. The statement of average dimensions is futile, as the variations in diameter and in observable length are great.

*Globules.*—Hinselmann<sup>11</sup> and Klingmüller<sup>12</sup> studied minute bodies which may occasionally be seen just beyond the tips of capillary loops. These globules are transitory, but may be observable on several suc-

10. Cutter, I. S., and Marquardt, G. H.: Studies in Capillary Fragility, Proc. Soc. Exper. Biol. & Med. 28:113 (Nov.) 1930.

11. Hinselmann, H.: Ein eigenartiges Zirkulationsphänomen bei einer Schwangeren und einer Eklampischen: Ein Beitrag zur Kenntnis der Kapillaren Blutungen, Deutsche med. Wchnschr. 48:254, 1922.

12. Klingmüller, M.: Capillarstudien; ueber die Scheitelkugeln der Nagelfalzcapillaren: III, Ztschr. f. d. ges. exper. Med. 55:808, 1927.

cessive days. Hinselmann concluded that they were a manifestation of the phenomenon of capillary bleeding, and that they represented a pathologic reduction of resistance of the walls of the capillaries. Klingmüller was able, however, to demonstrate the presence of these globules in normal patients and could produce them by forced running or by a moderate cooling of the skin. He therefore felt that they are not an abnormal finding, but that they prove that the capillaries of the nail cuticle are sometimes considerably wider than is to be expected from the extent of their blood stream. Von Thoma,<sup>13</sup> Herzog<sup>14</sup> and Tannenberg<sup>15</sup> substantiated this belief by work in animals. The globules may be due to pouches such as Herzog<sup>14</sup> noted in the capillaries of the tongue in frogs.

We have recently observed these globules in several capillary loops in one patient. In two of these loops it could clearly be seen that the



Fig. 5.—These capillaries are extremely tortuous for a man aged 30, in apparently perfect health, with a blood pressure of 126 systolic and 74 diastolic. This patient held the Intercollegiate Wrestling Championship, thus having put unusual strain on his circulation. We are not convinced of a definite relationship. It will be interesting to follow this patient for a period of years.

blood cells passing in the axial stream would catch the edge of the small clump of cells making up the globule and rotate the clump. Occasionally the clump would be caught in the axial stream and disappear, but shortly a new clump would be thrown off into the tip of the lumen and would rotate. We consider this definite proof that Klingmüller is correct in his belief that these capillaries may be much wider than can be observed under ordinary conditions.

13. von Thoma, R.: Die experimentell-mathematische Behandlung des Blutkreislaufes, in Abderhalden: Handbuch der biochemischen Arbeitsmethoden, Berlin, Urban & Schwarzenberger, 1909-1910, vol. 4, p. 1103.

14. Herzog, F.: Endothelien der Froschzunge als Phagocyten und Wanderzellen, *Ztschr. f. d. ges. exper. Med.* **43**:79, 1924.

15. Tannenberg, J.: Ueber die Kapillartätigkeit, *Verhandl. d. deutsch. path. Gesellsch.* **20**:374. 1925.

*Physiology.*—1. Function: The function of the capillaries is to permit an easy exchange of gases and fluids essential to the metabolism of the surrounding tissues. The rate of this exchange depends on several factors, one of which has been discussed, namely, the very thin capillary wall.

A second factor is the rate of flow of the blood through the capillaries. This factor also varies in different normal persons and to some degree in different capillaries in the same person. It varies greatly in each person under varying body and environmental conditions. Normally, the flow may be interrupted, and under changing conditions a varying number of capillaries may be in action. If the conditions remain unchanged (room temperature with hand at level of heart), it has been our observation that approximately the same number of capillaries and the majority of the same capillaries remain in action in a given field. Within these, the flow may be continuous over long periods of time, or it may flow, stop, and flow again. Noting great changes in the percentage of time that the flow was actually taking place, we have used what we term a "two minute flow test." For this test, large, easily defined capillaries are used in which blood cells are constantly present. Vessels which contract and disappear are not suitable. The number of seconds of flow and of stoppage are counted in a two minute (one hundred and twenty second) period, with the selected capillary under direct observation. A number of vessels are used to determine the averages and the extremes in a given patient. We have found that, under the foregoing conditions, normal variations in the period of stoppage average from fifteen seconds to zero in two minutes (one hundred and twenty seconds), whereas pathologic conditions may produce a period of stoppage as high as sixty-four seconds in one hundred and twenty seconds. In certain conditions of vascular spasm, no flow may be noted in a two minute period. In our patients with high blood pressure we rarely have seen stoppage of the flow in the large, well defined capillaries. Changes found in other conditions are being studied. The test provides a rough estimation of the constancy of flow, and examples of its practical value will be quoted later.

Stewart<sup>16</sup> estimated that, traveling at the rapid rate of 0.5 mm. per second, it would take 1 c.mm. of blood over six hours to pass through a capillary 10 microns in diameter. This slow process explains the necessity for the small arteriovenous anastomoses to accomplish rapid changes in the temperature of the skin.

2. Contractility: The ability of the capillaries to contract independently or to produce peristaltic movements have long been debated points.

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16. Stewart, G. N.: *Manual of Physiology*, London, Baillière, Tindall & Cox, 1895, p. 59.

The work of Lewis<sup>17</sup> and his co-workers would tend to indicate that the capillaries and the venules are capable of active contraction. These vessels are capable of exerting a force when fully contracted which resists the full entry of blood into them up to a pressure of from 90 to 100 mm. of mercury. When dilated, they are able, by contracting, to expel their contents against internal pressures of at least from 50 to 60 mm. of mercury. This means that these vessels must be of almost as great import as the arterioles in influencing circulatory events.

Hooker,<sup>18</sup> after an exhaustive review of the literature and his own studies,<sup>19</sup> concluded that the capillary bed had the ability to respond to the local needs of the tissue by dilatation when the conditions of the tissue tend toward asphyxiation and by constriction when the local needs have been satisfied.

The capillary bed is responsive to chemical influences by local reactions, usually by dilatation (only in special or pathologic cases by general reactions), and to nervous stimulation usually by constriction, over the body as a whole. It is therefore likely that beyond the arterioles the capillaries and venules function actively, thereby participating directly in vascular reactions. Further studies are necessary to establish this as a fact.

In this paper no attempt will be made to discuss in detail the reactions of the capillaries to various drugs and to foreign substances or to trauma.

If the capillaries are capable of active contraction, it is important to determine whether they aid in the propulsion of blood by peristaltic waves. Klingmüller<sup>20</sup> felt that the convolutions which are observed along the sides of the blood stream and which have been attributed to the peristaltic contraction of the walls of the capillaries by Kylin<sup>21</sup> and others are gaps in the flow of the blood cell columns or bulgings in the instance of over-filled capillaries. Our observations have led us to agree with Klingmüller on this point.

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17. (a) Cotton, R. F.; Clade, J. G., and Lewis, T.: Observations upon Dermatographism with Special Reference to the Contractile Power of the Capillaries, *Heart* **6**:227, 1915-1917. (b) Lewis, T.: The Force Exerted by the Minute Vessels of the Skin in Contracting, *ibid.* **11**:109, 1924; The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927. (c) Lewis, T., and Haynal, I.: Observations Relating to the Tone of the Minute Vessels of the Human Skin, *ibid.* **14**:177, 1928.

18. Hooker, D. R.: Evidence of Functional Activity on the Part of the Capillaries and Venules, *Physiol. Rev.* **1**:112, 1921.

19. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Micro-Capillary Tonometer, *Am. J. Physiol.* **52**:136, 1920.

20. Klingmüller, M.: Capillarstudien; I. Mitteilung zur Frage der Capillar-peristaltik, *Ztschr. f. d. ges. exper. Med.* **46**:94, 1925.

21. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.

3. Pressure: Many methods for the determination of the capillary blood pressure in man have been advanced since Roy and Brown<sup>22</sup> first published their fundamental observations in 1878. By these methods the normal capillary blood pressure has been determined to be from 7 to 70.5 mm. of mercury. Friedenthal<sup>23</sup> was justified in his conclusions that in 1922 the determination of capillary pressure by most of the existing methods was of little practical significance. The principle of the von Kries<sup>24</sup> method was used in most of the methods up to 1922. This consisted in applying a small glass plate to the skin and determining the pressure necessary to produce paling. We now know that the capillary flow may still be active at such a point, and that the color of the skin is largely controlled by the venous plexuses lying in the dermis. Von Kries published his normal readings as 37.7 mm. of mercury. Hough and Ballantyne,<sup>25</sup> using the same method, published from 40 to 50 mm. of mercury as their normal readings. Kylin,<sup>26</sup> in 1919, and Danzer and Hooker,<sup>19</sup> in 1920, introduced methods by which the flow of blood in the capillaries is observed while the pressure is being taken. The Danzer-Hooker capillary tonometer (described in detail in their communication) permits the observer to increase the pressure gradually until he notes a stoppage in capillary flow. There may then be a to-and-fro-movement of the blood, or it may even flow in the reverse direction. As the pressure is lowered, the point at which the blood flow resumes its forward movement is accepted as the capillary pressure. The average findings of various workers using this method have agreed closely, varying between 19 and 26 mm. of mercury. Our average normal readings have fallen within these limits.

A new tonometer has been demonstrated during the 1931 Graduate Fortnight of the New York Academy of Medicine by Strax and DeGraff. The capillaries are under direct observation with this method also. Strax and DeGraff suggested as the capillary pressure point the pressure at which the blood flow slows as it passes through the lumen. We feel that the use of this end-point would increase the many variables to a considerable degree, as the blood flow is constantly slowing and

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22. Roy, C. S., and Brown, J. G.: The Blood Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, *Arch. f. Anat. u. Physiol. (Physiol. Abt.)* 1878, p. 158; *J. Physiol.* 2:323, 1879.

23. Friedenthal, H.: Ueber Kapillardruck Bestimmung, *Ztschr. f. exper. Path. u. Therap.* 79:222, 1917.

24. von Kries, N.: Ueber den Druck in den Blutcapillaren der menschlichen Haut, *Arb. a. d. physiol.-anstalt-Leipzig* 10:69, 1875.

25. Hough, T., and Ballantyne, B.: Preliminary Note on the Effects of Changes in External Temperature on the Circulation of Blood in the Skin, *J. Boston Soc. M. Sc.* 3:330, 1899.

26. Kylin, E.: Proceedings, Ninth Nordiske Congress of Internal Medicine, Copenhagen, 1919.

speeding up again. Frequently it slows to the point of stoppage. We have found that when the blood flow has been stopped by pressure and that pressure is released, the blood immediately begins to flow again (with rare exceptions). We therefore agree with Danzer and Hooker that the point of pressure at which the flow recommences tends to introduce fewer inaccuracies and should be accepted as the capillary pressure when taken by such methods.

Landis<sup>27</sup> recently introduced a method for the determination of capillary pressure which from the point of view of scientific observation will probably force all other methods now known into discard. He cannulates the capillaries by means of fine glass pipets, and by direct observation determines the exact point at which the corpuscles oscillate in and out of the tip of the pipet. The pressure rises in one third of the capillaries for one or two minutes, but returns to normal in from three to five minutes.

Whereas all other methods determine one figure as the capillary pressure, Landis has been able to demonstrate that there is a definite

*Capillary Pressure Readings of Landis*

Pressure Measured	Position of Pipet	Number of Observations	Capillary Pressure, Mm. Hg	
			Range	Average
Arteriolar limb.....	A	125	21-48	32
Summit of loop.....	B	19	15-32	20
Venous limb.....	C	99	6-18	12

gradient of pressure fall in the capillary loop. His readings, based on different portions of the loop, are shown in the table. Three readings taken in the same loop at points A, B and C confirm these figures. The importance of this gradient in controlling tissue fluids will be discussed later.

The figures obtained by the Danzer-Hooker tonometer seem to represent about an average of the three figures. The method of Landis requires an elaborate technic, so that other methods may continue in use for rough estimations of capillary pressure, but they should not be accepted as giving the true picture of the pressures within a capillary. For the purpose of accurate comparison, all pressure readings should be taken with the hand at the cardiac level and under standard conditions.

4. Permeability: The permeability of the capillaries is of great importance in its effect on the fluid balance of the body. Ganzzen<sup>28</sup>

27. Landis, E. M.: (a) Micro-Injection Studies of Capillary Blood Pressure in Human Skin, Heart 15:209, 1930; (b) Micro-Injection Studies of Capillary Blood Pressure in Raynaud's Disease, ibid. 15:247, 1930.

28. Ganzzen, Max: Ueber die Durchlassigkeit der Haargefässwand beim Menschen, München. med. Wchnschr. 69:263, 1922.

first introduced the method now in use for its determination. A small cantharides plaster is applied to the arms of the patient, and the transudate in the blister is examined by a refractometer. The contents of the blister normally show albumin 5.04 per cent (Reiss exudate table). Blood serum normally contains 8.06 per cent albumin (regular serum table). Petersen and Willis<sup>29</sup> suggested a formula for the permeability ratio:

$$\text{Permeability ratio} = \frac{\text{percentage of blister protein}}{\text{percentage of serum protein}}$$

Since the time necessary for the production of the blister varies greatly in pathologic conditions, the following formula was deduced:

$$\text{Inflammatory index} = \frac{\text{permeability ratio}}{\text{blister time}}$$

Normal blister time is from seven and one-half to eight hours. The results of Petersen and Willis,<sup>29</sup> Petersen and Levinson<sup>30</sup> and Chasanow<sup>31</sup> showed the average permeability ratio to equal from 0.62 to 0.68.

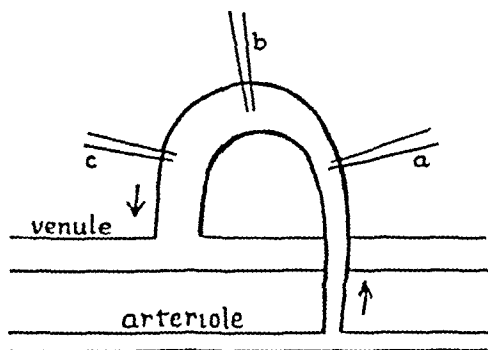


Fig. 6.—Drawing illustrating Landis' points for reading capillary pressure.

The permeability of the capillary walls is subject to the laws of filtration, diffusion and osmosis and is also affected by the ionic concentration at the cell membranes in the blood, the state of the endocrine system, and especially, according to Bruck,<sup>32</sup> Kayikawa,<sup>33</sup> Petersen and Willis<sup>29</sup> and Chasanow,<sup>31</sup> the state of the visceral nervous system.

29. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch. Int. Med.* **38**:663 (Dec.) 1926.

30. Petersen, W. F., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients, *Arch. Path.* **9**:205 (Jan.) 1930.

31. Chasanow, M.: Permeabilität der Hautkapillaren bei Nervenkranken, *Monatschr. f. Psychiat. u. Neurol.* **75**:62, 1930.

32. Bruck, C.: Experimentelle Beiträge zur Aetiologie und Pathogenese der Urticaria, *Arch. f. Dermat. u. Syph.* **96**:241, 1909.

33. Kayikawa, J.: Untersuchungen über die Permeabilität der Zellen: X, *Biochem. Ztschr.* **133**:391, 1922.



Rous, Gilding and Smith,<sup>34</sup> Smith and Rous,<sup>35</sup> and McMaster, Hudack and Rous<sup>36</sup> showed by the intravenous use of dyes (Chicago blue 6 B, trypan red, trypan violet and trypan blue) that the permeability of capillaries in the skeletal muscles of mammals increases progressively along their course and is greatest when they pass into the least venules. This gradient helps to equalize the opportunities to cells along the course of the capillaries. It is probably due to a structural differentiation along the capillary. The venules are even more permeable. Slight increases in venous pressure increase the outward passage of dyes from the venules and the venous limb of the capillaries. As this pressure is increased, the greater permeability extends along the capillary toward the arteriolar end. It is impossible to say whether this is due to secondary dilatation of the capillaries producing an increase in the surface area with local permeability due to thinning of the wall or to heightened hydrostatic pressure producing active filtration. Probably both factors contribute. If venous pressure is increased to the point of nearly equaling the arteriolar pressure producing forcible dilatation of the capillaries, the gradient of vascular permeability disappears. These workers feel that transudation through small venules is more important for the rapid development of edema of the skin as a result of increased venous pressure than is transudation through the capillaries.

In heart disease with failure, for instance, the small vessels are caught between the arterial pressure and an abnormally high venous one. Most of the edema fluid actually accumulates in the subcutaneous tissue. It seems more likely, though not proved, that it seeps back secondarily from the skin rather than arises as a result of fluid escaping from the relatively infrequent subcutaneous vessels.

Edema following vascular injury by heat or cold, on the other hand, develops mainly as a result of loss of fluid by the capillaries, the permeability of which rises to equal or exceed that of the venules.

Hoff and Leuwer<sup>37</sup> experimented with the use of 1 per cent solution of congo red intravenously, and found that this high molecular dye practically did not penetrate the wall of the capillary, under normal

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34. Rous, P.; Gilding, G. P., and Smith, F.: The Gradient of Vascular Permeability, *J. Exper. Med.* **51**:807, 1930.

35. Smith, F., and Rous, P.: Conditions in Frog and Chicken Muscle and in the Mammalian Diaphragm, *J. Exper. Med.* **53**:195, 1931; Gradient Along the Capillaries and Venules of Frog Skin, *ibid.* **53**:219, 1931.

36. McMaster, P. D.; Hudack, S. S., and Rous, P.: The Relation of Hydrostatic Pressure to the Gradient of Capillary Permeability, *J. Exper. Med.* **55**:203, 1932; McMaster, P. D., and Hudack, S. S.: The Vessels Involved in Hydrostatic Transudation, *ibid.* **55**:417 and 431, 1932.

37. Hoff, F., and Leuwer, W.: Experimentelle Untersuchungen über die Permeabilität der Capillaren des Menschen, *Ztschr. f. d. ges. exper. Med.* **51**:1, 1926.

conditions, but that the same dye penetrated the wall in an inflamed field. Therefore, there is an increase in permeability of the capillary walls in the inflamed region.

The production of a wheal by the injection of various substances such as sodium chloride, potassium chloride, calcium chloride, magnesium chloride, casein and a nonspecific milk preparation also produces changes in the permeability of the capillaries to congo red.

5. Osmosis: The downward gradient of capillary pressure demonstrated by Landis appears to be of great significance in the control of fluid exchange. Determinations of the osmotic pressure of the colloid for human serum and plasma vary between 23 and 28 mm. of mercury (Govaerts,<sup>38</sup> Serr,<sup>39</sup> Schade and Claussen,<sup>40</sup> Iversen and Nakazawa,<sup>41</sup> Verney<sup>42</sup>). Dieter<sup>43</sup> gave as his figure 31 mm. of mercury.

The figures of Landis show that the pressure in the arterial limb of the capillary under normal conditions is greater than the osmotic pressure of the plasma proteins; hence, other factors being equal, the direction of flow should be outward from the capillary wall. The venous limb has a pressure below the normal osmotic pressure of the plasma proteins; hence the flow should be inward through the wall of the capillary. Such conditions as increase the capillary pressure throughout a capillary above the osmotic pressure of the plasma (example, heating of the skin) result in greatly increased rates of filtration and production of lymph. With dilatation of the arterioles and capillaries, the arteriolar fraction of peripheral resistance is reduced, and as a result the level of capillary pressure in both the venous and the arteriolar limbs of the capillary loop is raised to the point where outward filtration may take place in both portions of the loop. In this instance we have increased pressure plus increased outward filtering area with a decreased absorption area, the result being increased tissue fluid plus increased lymph flow.

Capillary pressure is thus clearly demonstrated to be an important factor in the normal and abnormal interchange of fluid between the

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38. Govaerts, Paul: Recherches cliniques sur le rôle de la pression osmotique des protéines du sang, dans la pathogenie des oedemes et de l'hypertension artérielle, *Bull. Acad. roy. de méd. de Belgique* **4**:161, 1924.

39. Serr, H.: Blutbeschaffenheit und Glaukom, *Arch. f. Ophth.* **114**:393, 1924.

40. Schade, H., and Claussen, F.: Der onkotische Druck des Blutplasmas und die Entstehung der renal-bedingten Oedeme, *Ztschr. f. klin. Med.* **100**:363, 1924.

41. Iversen, Paul, and Nakazawa, Fusakichi: Ueber die Biochemie des Filtrations Odems, *Biochem. Ztschr.* **191**:307, 1927.

42. Verney, E. B.: The Osmotic Pressure of the Proteins of Human Serum and Plasma, *J. Physiol.* **61**:319, 1926.

43. Dieter, Walter: Ueber den Zusammenhang zwischen osmotischem Druck, insbesondere Kapillardruck und Augendruck nach neuen experimentellen und klinischen Untersuchungen, *Arch. f. Augenh.* **96**:179, 1925.

blood and the tissue spaces. The downward gradient of capillary pressure and the upward gradient of permeability must act in proper balance for the equalization of opportunity for all cells.

6. Response to Heat, Cold, Stroking and Changes in Altitude: For a number of years Lewis<sup>44</sup> has been studying the effects of slight injuries on normal capillaries. He has reached the following conclusions:

1. Light stroking of the skin produces white lines due to active contraction of the capillaries and venules of the skin.

2. Heavy stroking of the skin produces red lines due to active dilatation of the capillaries and venules, also possibly the terminal arterioles.

(a) The surrounding flush is due to independent and widespread dilatation of the arterioles brought about by local axon reflex.

(b) The wheal is due to an outpouring of fluid from the vessels secondary to a local increase of the permeability of the vessel walls independent of dilatation and uncontrolled by the nervous system. A dilution of 1:30,000 of histamine when injected into the skin produces the same triple response. Probably the same fundamental cause is at work, namely, a histamine-like substance (termed the H substance).

The effect of increased environmental temperature is the dilation of the capillaries with an increase in the rate of blood flow through them. With fever, these effects are greatly accentuated. When the environmental temperature is lowered slowly, the number of capillaries remaining open and active usually decreases and the rate of flow usually slows. However, we have found that if the part is suddenly chilled, as by dipping in ice water, the effect in some cases may be the activation of many more capillaries with a markedly increased rate of flow. This is apparently an attempted compensatory reaction.

Although the theoretical freezing point of skin is about  $-0.6^{\circ}\text{C}$ . (as physiologic solution of sodium chloride), arctic explorers may be exposed to  $-20$  or  $30^{\circ}\text{C}$ . without frostbite. The relative moistness and greasiness of the skin predispose to a protective supercoating.

Vannotti,<sup>45</sup> of von Willer's laboratory, studied the effects of altitude on normal capillaries. He has found that with changes in altitude (hence atmospheric pressure) up to 4,560 meters, as with changes in temperature, and effects of the toxic products of metabolism produced by exercise and fatigue, certain changes take place in the diameter and form of the capillaries, and also in the rate of flow through them. Morphologically, it is interesting and important that the characteristic

44. Lewis, T.: Abstract of Four Croonian Lectures, Brit. M. J. 2:61 (July 10) 1926. Lewis,<sup>17d</sup>

45. Vannotti, A.: Die Wirkung des Hohenklimas auf die Hautcapillaren der Menschen, Klin. Wchnschr. 6:253 (Feb. 7) 1931.

shape of each capillary loop remains recognizable despite the action of these various factors. Definite changes can, however, be noted in separate parts of the loops. With increased altitude, the capillaries become dilated and fill with blood. This change is undoubtedly associated with the transient polycythemia commonly noted in mountain climbers at high altitudes. The capillaries apparently attempt to approximate their condition at normal level but are affected by the increased heart rate and probably other little understood factors. The reestablishment of normal appearance and diameter on return to sea level after a variable time at a high altitude takes place by degrees and follows the changes which can be noted in the organism as a whole in its transition to normal function under the new conditions.

#### CAPILLARY CHANGES IN DISEASE CONDITIONS

*High Blood Pressure.*—While a markedly increased blood pressure is frequently associated with an increase in tortuosity of the capillaries



Fig. 7.—The variability of the appearance of capillaries in cases of hypertension. The tortuous loops are from a patient with an average blood pressure of 190 systolic and 120 diastolic. The straight loops are from a patient with the unusual blood pressure of 300 systolic and 190 diastolic. In both cases the flow was very rapid and uninterrupted. The arterial limbs were constricted and the outlines distinct.

—definitely more pronounced than would be expected from the age of the patient—there are many exceptions to this rule. We cannot confirm Grzechowiak,<sup>46</sup> who described characteristic changes occurring in different stages of the disease. We have not seen an increase in tortuosity above normal in patients with uncomplicated hypotension. Therefore, we may assume that some factors which are present in patients with hypertension may produce tortuosity under certain conditions, and that these conditions or these factors are practically never found in patients with uncomplicated hypotension. One cannot say what these

46. Grzechowiak, F.: Der Kapillardruck, besonders während der Schwangerschaft, Ztschr. f. Geburtsh. u. Gynäk. 87:128, 1924.

factors are at present. Boas and Mufson<sup>47</sup> classified cases of hypertension into two groups which cannot be differentiated clinically: those with high capillary blood pressure and those with normal or low capillary blood pressure. The capillaries in these cases may appear as tortuous with low capillary pressure as with high pressure. As an example, in beds alongside of each other at the New York Post-Graduate Hospital were a man aged 39 and one aged 82. The young man was suffering from malignant hypertension. His blood pressure averaged 220 systolic and 140 diastolic; his arteries were sclerosed wherever palpable, his capillaries were very tortuous, but not markedly dilated, and the capillary pressure averaged 26 mm. of mercury (Danzer-Hooker tonometer). The old man's blood pressure varied between 188 systolic and 92 diastolic and 140 systolic and 70 diastolic. His peripheral arteries were not unusually sclerosed, even for a man fifteen years younger, and his capillaries were much less tortuous than the young man's. In fact, they would have been normal for a man fifteen years younger than he was. His capillary pressure averaged 22 mm. of mercury. The readings of the capillary pressure for both were within normal limits.

High capillary pressures were present in seventeen of forty-five cases of hypertension reported by Boas and Mufson.<sup>47</sup> The mortality in this group was much higher (eight of seventeen, or 47 per cent) than in the group with low readings (five of twenty-eight, or 17.8 per cent). Four patients with high and four with low capillary pressure came to autopsy. No characteristic differences were noted.

In general, the most significant relationship established was between the capillary pressure and the diastolic blood pressure. However, many of the patients of Boas and Mufson and many of our patients with a high diastolic pressure have had a normal capillary pressure. A much larger group of patients must be studied to establish this work satisfactorily.

These workers reported one unusual case showing a normal blood pressure from 125 systolic and 95 diastolic to 105 systolic and 70 diastolic and with a high capillary pressure averaging about 33 on the basis of many readings. Capillary pressure bears no fixed determinable relationship to arterial or venous pressure, and workers such as von Farkas<sup>48</sup> and Nakazawa and Izumi,<sup>49</sup> who attempt, to calculate the

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47. Boas, K., and Mufson, I.: The Capillary Blood Pressure in Arterial Hypertension and in Nephritis, *J. Lab. & Clin. Med.* **9**:152 (Dec.) 1923.

48. von Farkas, G.: Ist das Oedem ein Resultat der Capillarsekretion, *Ztschr. f. d. ges. exper. Med.* **62**:35, 1928.

49. Nakazawa, Fusakichi, and Izumi, Jiro: Studien über den kolloidosmotischen Druck des Bluts im normalen und pathologischen Zustand, *Tohoku J. Exper. Med.* **16**:341, 1930.

capillary pressure from either of these figures, can only draw unjustified conclusions.

Petersen found nine patients with hypertension with a systolic pressure of over 140 in the group with less permeability; four patients showed increased permeability.

Weiss and Frazier<sup>50</sup> found no definite increase in the number of active capillaries per square millimeter of body surface in persons with hypertension as compared with the normal controls. In studying the number of active capillaries in a unit area of skin, however, it is difficult to estimate other important signs of activity, such as the rate of flow and dilatation or constriction of the capillary limbs. This difficulty is due to the fact that only the tips of the capillaries can be seen, except in such special areas as the junction of the skin and mucous membrane of the lips and at the nail fold.

The rate of flow through the capillaries of most hypertensive patients is increased, and with the "two minute test" previously described it is rare to find a stoppage longer than four seconds in any of the large capillaries. Often with prolonged observation no stoppage can be noted.

*Low Blood Pressure.*—Conversely with high blood pressure, a consistently low blood pressure is usually associated with long, straight, dilated capillary loops. Through these the blood cells flow slowly, frequently stopping. The capillary pressure is low or normal. In one case, the average stoppage in the "two minute flow test" was sixty-six seconds. This patient was referred to us because of tingling and burning of the fingers, for which no definite cause could be found by the internist or neurologist. Her blood pressure at that time was 85 systolic and 65 diastolic, but many persons with low blood pressure do not have the symptoms of which this patient complained. She was put on a regimen of alternating hot and cold water baths twice a day and sent to the seashore to tone up generally. She returned after five weeks with complete freedom from her symptoms. At this time her average stoppage was four seconds. Her blood pressure was 110 systolic and 65 diastolic.

We do not feel that the difference of a few seconds more or less has any significance in the two minute flow test. When the blood is flowing through major capillaries less than half of the time by measurement, as in this case, we feel that such a fact is important and should be noted according to some standard. Ten counts should be made on different prominent capillaries and an average obtained.

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50. Weiss, S., and Frazier, W.: The Density of the Surface Capillary Bed of the Forearm in Health, in Arterial Hypertension, and in Arteriosclerosis, *Am. Heart J.* 5:511 (April) 1930.

Essential low blood pressure may conceivably be due to capillary dilatation and stasis secondary to a toxin. Histamine shock, as well as other types of shock, present the same picture. Friedlander<sup>51</sup> expressed the belief that the H substance may be responsible.

*Acute Nephritis.*—It seems probable in view of the studies of many workers that acute glomerulonephritis should be looked on as a manifestation of a pathologic condition in which the capillaries generally show evidence of damage. During the acute stages there is a consistent elevation in capillary pressure (Kylin<sup>52</sup> and Mufson<sup>53</sup>). This returns to normal with convalescence. Kylin found that in scarlet fever with complicating acute glomerulonephritis the capillary pressure increases successively for several days before the onset of albuminuria. In some cases the capillary pressure increased and subsided without the presence of albuminuria. In cases with no increased pressure, nephritis did not



Fig. 8.—This illustrates the usual straight, moderately dilated capillaries seen in a patient with uncomplicated hypotension. The flow was slow with frequent stoppage. The average blood pressure was 100 systolic and 60 diastolic.

develop. Pathologically, the primary lesion of the kidney is found in glomerular capillaries. Hückel<sup>54</sup> was of the opinion that the reason that all of the glomeruli are not affected is the fact that many are inactive a large portion of the time, and hence would not be exposed to toxins circulating in the blood. The active glomeruli would be the first affected. The edema seen must be due to increased permeability of the capillary walls, increased capillary pressure or decreased osmotic pressure of the serum proteins. The last is probably secondary to the loss of albumin, since it remains normal in mild cases. The cause of

51. Friedlander, A.: Address at Graduate Fortnight of New York Academy of Medicine, New York Post-Graduate Medical School, Oct. 19, 1932.

52. Kylin, E.: *Die Hypertoniekrankheiten*, Berlin, Julius Springer, 1930.

53. Mufson, I.: A Study of the Capillary Pressure in Nephritis and Hypertension, *Am. J. M. Sc.* **183**:632 (May) 1932.

54. Hückel, R., cited by Kylin.<sup>52</sup>

these capillary changes is unknown, but it seems likely that absorption of toxins from foci of infection plays a large rôle.

A similar diffuse capillary poisoning has been demonstrated by Heubner<sup>55</sup> with the use of gold chloride, resulting in dilatation with hematuria and edema.

No constant morphologic change has been noted in the capillaries in this condition. In our experience, the rate of flow and the constancy of flow have increased as would be expected with the increased pressure.

*Chronic Nephritis.*—The capillaries in chronic nephritis show increased tortuosity in many cases. This tends to increase with the duration of the disease and the hypertension present. In Mufson's<sup>53</sup> series there was a correlation between the capillary pressure and the degree of renal dysfunction. Nearly all of the cases with normal capillary pressure showed normal renal function, while those showing



Fig. 9.—Capillaries in a patient with marked generalized arteriosclerosis. They showed the typical "moth-eaten" appearance, with a slow flow and frequent stoppage.

increased capillary pressure showed increasingly impaired function. There were occasional exceptions both ways. These findings also point to a systemic capillary involvement, although in these cases it would seem to appear after the early changes in the kidney as evidenced by urinary findings.

In reference to contradictory data concerning the capillaries in hypertension and nephritis, Patzold<sup>56</sup> called attention to the fact that since the venous and capillary systems are from the same anlage, conflicting opinions may arise from studies of the capillaries without a consideration being given to the status of the venous system at that time.

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55. Heubner, Wolfgang: Ueber Vergiftung der Blutcapillaren, Arch. exper. Path. **56**:370, 1907.

56. Patzold, A.: Untersuchungen über das menschliche Venensystem, Deutsches Arch. f. klin. Med. **171**:89 (April) 1931.



*Senile Arteriosclerosis.*—In patients with hardening of the peripheral arteries and without any other demonstrable disease, we have noted no unusual degree of tortuosity. These cases fall into the senescent groups and are entitled to moderate tortuosity because of age. The blood flow becomes sluggish as the condition becomes more marked. The loops sometimes appear rather moth-eaten. Weiss and Frazier<sup>50</sup> found that no definite relationship existed between the number of capillaries active per millimeter of body surface, and the clinical evidence of arteriosclerosis or the age of the patients. They concluded that a reduction in number of visible surface capillaries per square unit cannot be held responsible for the changes in the skin with the advancing age and in arteriosclerosis. We have noted, however, that the rate and constancy of flow are frequently diminished in these cases, and such findings may well account for changes in the skin and elsewhere with age.

*Toxemia at Pregnancy.*—Capillary pressure in normal pregnancies is normal according to Grzechowiak<sup>57</sup> and Nevermann,<sup>58</sup> but with toxemias the capillary pressure tends to rise. Mufson<sup>59</sup> summarized three groups of patients as follows: (1) Normal gravida with normal capillary morphology and pressure. These mothers had uneventful deliveries and were delivered of normal children. (2) Women with hypertension but low capillary pressure readings during pregnancy. These mothers responded to conservative routine treatment. There was one fetal death. (3) Women with high capillary pressure readings during pregnancy. The course of the pregnancy was stormy and the response to treatment was poor in 70 per cent of the mothers, with resultant therapeutic induction of labor. Fetal death occurred in 50 per cent of these cases.

It is clear that high capillary blood pressure readings have a serious import for the mother and fetus.

*Polycythemia Vera.*—The active capillaries in polycythemia vera are increased in number. Brown and Giffin<sup>60</sup> and Brown and Sheard<sup>61</sup> studied this increase quantitatively with the following results: There

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57. Grzechowiak, F.: Die medikamentöse Beeinflussung des Kapillarkreislaufes am Fingernagelfalz, Monatschr. f. Geburtsh. u. Gynäk. **62**:7, 1923.

58. Nevermann, H.: Capillardruckmessungen, Klin. Wchnschr. **3**:1433 (Aug. 5) 1924.

59. Mufson, I.: The Capillary Pressure in the Toxemias of Pregnancy, Am. J. Obst. & Gynec. **15**:800, 1928.

60. Brown, G. E., and Giffin, H. Z.: Studies of the Vascular Changes in Cases of Polycythemia Vera, Am. J. M. Sc. **171**:157 (Feb.) 1926.

61. Brown, G. E., and Sheard, C.: Measurements of the Skin Capillaries in Cases of Polycythemia Vera and the Role of Those Capillaries in the Production of Erythrosis, J. Clin. Investigation **2**:423 (June) 1926.

was an average of from sixty-two to sixty-five open capillaries for each square millimeter of skin on the back of the hand (normal figure, from fifteen to forty). No marked variation was noted in any one subject.

By use of photomicrographs, the area of exposed capillary blood per unit area of skin was calculated. This ratio averaged 15 per cent in the cases of polycythemia vera, which is three times greater than the normal figure of 4.9 per cent. In our cases no increase in tortuosity has been noted. In fact, the loops are usually very straight. They appear to be filled and bulging with cells which move sluggishly through the lumen.

By way of contrast, a patient with a relative polycythemia secondary to a congenital cardiac condition (red blood cells 8,340,000; hemoglobin 111 per cent) showed markedly tortuous capillaries.

In the cases of true polycythemia the venous limb becomes especially dilated, which dilatation seems gradually to work back over the crest of

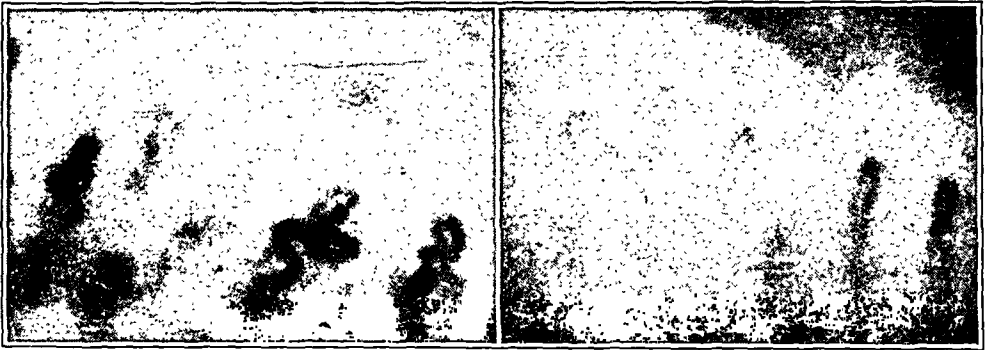


Fig. 10.—The straight capillaries are from a patient with polycythemia vera, with 10,000,000 red blood cells and 123 per cent hemoglobin. Dilatation extending from the venous side over into the arterial limb could be seen. The very tortuous and dilated capillaries are from a patient with congenital heart disease with secondary relative polycythemia, with 8,000,000 red blood cells and 128 per cent hemoglobin. We have never seen marked tortuosity in a case of uncomplicated polycythemia vera.

the loop. The arterial limb is usually normal and may even be slightly constricted.

In the cases which respond to treatment, the number of active capillaries decrease and they appear less prominently.

*Scleroderma.*—The capillaries in patients with scleroderma are difficult to study in the areas affected. They appear as irregular distorted vessels. Rarely are they seen as definite loops but rather as hazy shadows through which the blood flows slowly and stops when the environmental or body temperature is lowered. The blood then becomes cyanotic, but if the temperature is raised the flow is quickened and the blood becomes brighter red. Because of the texture of the skin, capillary pressure readings are not possible.

Brown, O'Leary and Adson<sup>62</sup> ascribed the marked impairment in the transparency of the skin to the following three factors: (1) the increased density in the skin, (2) perhaps the interference with flow of lymph and accumulation of the fluid and (3) pigmentation.

A major factor in a well advanced case is lack of blood in the skin. This lack of blood is probably due in a large measure to two factors: the increase in collagen, which results in shutting down of the capillaries and arterioles by pressure, and an excessive degree of vasospasm in the arterioles. The foregoing authors have demonstrated that sympathetic gangliectomy helps the condition as a whole and that the capillaries become much more prominent and active, hence, insuring an increased blood supply to the area involved.

*Raynaud's Disease.*—The capillaries of the nail bed in Raynaud's disease between attacks are long, dilated, characteristically atonic loops through which the blood flows slowly, frequently stopping. The number



Fig. 11.—Remarkable dilatation of the capillaries during the period of hyperemia in Raynaud's disease. As will be noted, the dilatation is most marked on the venous side.

open per field is greater than normal. The response to changes in temperature is marked. In a case described by Adson and Brown<sup>63</sup> after sympathetic gangliectomy the capillaries on the side on which operation had been performed were reduced to normal in number and appearance; the blood flow was regular and the blood red. The loops were more restricted, showing increased tonus.

Landis,<sup>27b</sup> using his micropipet, studied the changes in the capillary pressure in Raynaud's disease. During the period of spasm the capillary pressure at the summit of the loop falls to from 5 to 8 mm. of mercury. If the arterial inflow has stopped, this pressure is probably due to pressure in the veins of the hand or forearm.

62. Brown, G. E.; O'Leary, P., and Adson, A. W.: Diagnostic and Physiologic Studies in Certain Forms of Scleroderma, *Ann. Int. Med.* 4:531 (Dec.) 1930.

63. Adson, A. W., and Brown, G. E.: Raynaud's Disease of the Upper Extremities, *J. A. M. A.* 92:444 (Feb. 9) 1929.

During the first eight to twelve minutes of recovery, with its accompanying hyperemia, the capillary pressure rises, reaching maximal pressures of from 32 to 45 mm. of mercury, and then gradually falls to more normal readings. During the period of spasm, there are no pulsation in the pipet and no sensation of throbbing. During the period of hyperemia, there are marked pulsation and marked throbbing. During a normal period there are diminished pulsation and throbbing. The skin temperature is dependent on the room temperature during the period of spasm. With recovery, it rises definitely above room temperature gradually returning to normal.

During the spasm, the capillaries are sharply defined through flat tissues. During recovery, the outlines of the capillaries gradually become blurred, and the skin at the base of the nail becomes visibly raised. This is due to the accumulation of fluid in the hyperemic tissue.

Probably the high pressure recorded plus increased permeability due to asphyxia explains the swelling of the fingers during recovery.

In studies to determine the situation of the vascular spasm in Raynaud's disease, Landis found that when a pneumatic cuff was inflated to 40 mm. of mercury in normal persons the capillary pressure rose to an equal height within from three to four minutes. In Raynaud's disease, the rise was very slow. During the first four to five minutes there was no change, and only after thirteen to fifteen minutes was the capillary pressure equal to that in the armlet. This showed that inflow is retarded on the arterial side. When the pressure of the cuff was released, the capillary pressure fell so rapidly that it was almost normal in one minute.

The facts that the veins in the hands are small when the hands are cold and blue and that the pressure falls rapidly under the conditions described in the foregoing paragraph show that the obstruction offered by these veins is insufficient to interfere with outflow from the capillaries.

These observations, together with the low pressures observed during spasm, show that the stasis in Raynaud's disease is not due to venous congestion. It is due to changes in the arterial side of the loop.

*Thrombo-Angiitis Obliterans—Buerger's Disease.*—The pronounced rubor which is noted in this and other diseases marked by defective circulation in the deeper vessels is secondary to the condition of the capillaries and venules. In agreement with Brown, Allen and Malhorner,<sup>64</sup> we find that these cases seem to be divided according to capillary changes into two groups. In the first group—without vasoconstrictor phenomena—the capillaries are moderately dilated and the number open

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64. Brown, G. E.; Allen, E. V. A., and Malhorner, H. R.: *Thrombo-Angiitis Obliterans*, Philadelphia, W. B. Saunders Company, 1928.

and active is increased. The flow is slow, often stopping. It may cease for an entire two minute period. If the extremity is lowered below the heart level, the rubor increases and more capillaries and venules can be seen to open. Cyanosis occurs with further slowing of the capillary flow.

The second group with visible vasoconstrictor phenomena have been more common in our series. At room temperature or colder, there is a marked constriction of the capillaries. Only a few per field may be indistinctly visible. Photographing these capillaries has been especially difficult, an indistinct blur representing each capillary. The flow is slow and the blood becomes cyanotic. If the environmental temperature is raised, capillary flow slowly increases in rate and a few more capillaries open. The reaction is slow, and the increase is not great until the temperature reaches a high level. The flow does not become regular, but is jerky with many gaps. The foregoing authors have

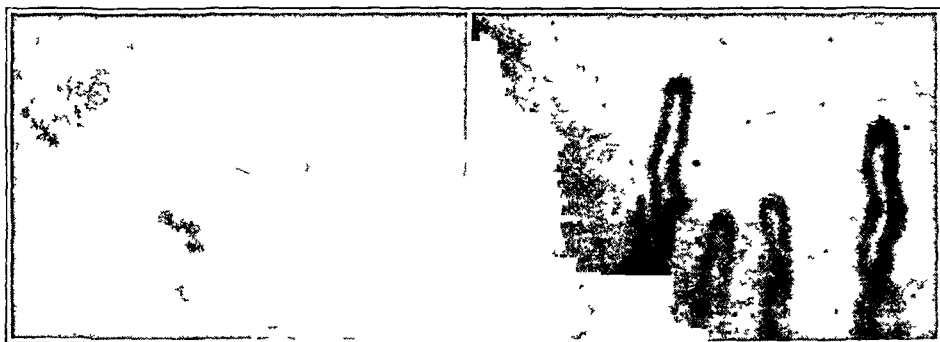


Fig 12.—Variations in appearance of the capillaries in arthritis. These and the ones in the photograph showing the most marked anastomoses (fig. 2) are from Dr. Kovacs' series of cases of arthritis.

suggested that this effect may be due to a precapillary arteriole opening and closing, allowing small spurts of blood to pass through. Tests with epinephrine, pituitary and histamine showed that the capillaries in this condition are not paralyzed, but require greater stimuli to produce vasoconstriction. Many of these small vessels show actual thrombosis on pathologic section.

*Erythromelalgia.*—The capillary loops in erythromelalgia may be gigantic, grotesque and irregular in form. The blood flow is exceedingly sluggish, and stagnant pools of blood may form at the ends of the capillaries, helping to produce the changes in the color of the skin seen in this condition.

*Arthritis.*—There has been great disagreement concerning the characteristics of the capillaries in arthritis. Kovacs,<sup>65</sup> working in the

65. Kovacs, J, with the collaboration of Wright, I. S., and Duryee, A. W : The Surface Temperature and Minute Blood Vessels of the Skin in Arthritis, J. A. M. A. 100:1018 (April 1) 1933.

capillary laboratory at the New York Post-Graduate Medical School and Hospital, recently completed a detailed study of this subject. He concluded that poor capillary circulation could not be established as the direct cause of the pathologic changes accompanying this disease. The only consistent findings were the decrease in number and the constriction of capillaries in fingers with Heberden's nodes or swollen joints (this could be accounted for on the basis of mechanical pressure) and a lowered surface temperature. In other cases there was nothing characteristic in the number, appearance, rate or consistency of flow. His cases were subdivided into rheumatoid arthritis, osteo-arthritis and non-articular rheumatism and were studied separately. It is conceded that the condition of the capillaries of the skin may not indicate the condition of the capillaries within a bone or a joint. It seems that conclusions drawn on the assumption that comparisons can be made should be

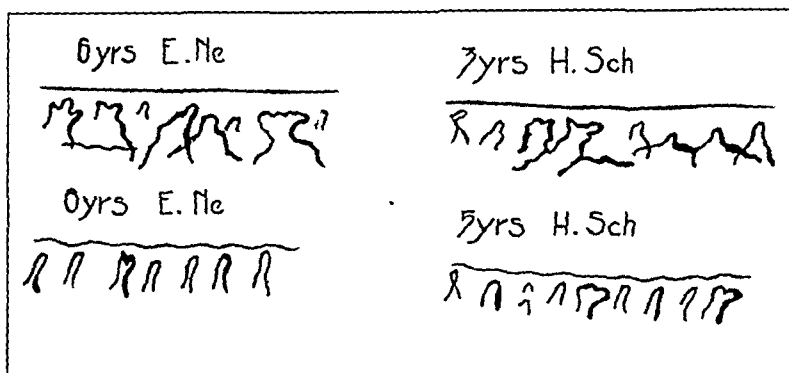


Fig. 13.—The effect of the administration of thyroid extract to cretins (Jaensch).

accepted with great skepticism. Kovacs' study should help to reestablish balance in this field of endeavor.

*Relationship Between Capillary Development and Mental Development.*—Jaensch and co-workers<sup>66</sup> have been engaged in studies of the developmental processes of the capillaries and their psychophysical relations for some years past. The capillaries of normal infants form a network running horizontally under the surface of a smooth corium. During the course of the first year of infant life, these vessels tend to change from the horizontal capillaries without loops to a more vertical position, forming loops that go up into papillae which rise up from the corium. A difference can then be noted between the arterial and the venous limbs. Parallel with these capillary developments is the development of the child. With stunting of capillary development, it was observed that the child is likewise stunted in all other respects. Jaensch was of the opinion, therefore, that the development, restriction

66. Jaensch, W.; Wittneben, W.; Hoepfner, T.; von Leupoldt, C., and Gundermann, O.: *Die Hautkapillarmikroskopie*, Halle, A. S., Carl Marhold, 1929.

of development or diversion of development of the capillary field is a fair indication of the state of the individual, especially during the earliest periods of life.

The capillaries of cretins with a low degree of development, i. e., a 16 year old cretin girl who showed the intelligence of a backward 5 year old child and was bodily helpless, show the very early form of capillary development described, which is termed the "archicapillary form." In other words, parallel with the lack of capillary development there has been a lack of mental and physical development. If thyroid given to these children at an early stage is successful in improving their mental and physical status, it can be observed that the capillaries likewise become more normal. If the patient is too old to yield to treatment, the capillaries do not improve so markedly, although they may show relatively more improvement than the mental or the physical status. Jaensch felt that the prime cause for this state of abnormality of the capillaries rests in the inter-relationship between the midbrain, which plays the chief rôle, and the endocrine glands, of which the thyroid gland is the most important. It was found that in districts in which goiter is prevalent, such as Hessen, capillary differentiation is slower even in a normal child than it is in nongoitrous districts, such as Frankfort-on-the-Main. In the latter city the differentiation of infantile capillaries reaches the normal hairpin form in the sixth month of life.

A comparison of the capillaries of pupils of a normal elementary school with those of pupils in an accessory school for the mentally deficient gave the following figures: In the normal school of twenty-six pupils, only three showed capillary restriction, whereas in the accessory school of twenty-one pupils, fourteen showed capillary restriction. From this it would seem that not all feeble-minded children have abnormal capillaries and some normal children may have abnormal capillaries.

Among pupils of a normal school in a cretinous district, the percentage of children with restricted capillaries was almost as high as that among pupils of an accessory school in a healthy district.

Gesell<sup>67</sup> stressed the importance of this early developmental stage as follows: "One month of early childhood is of dynamic importance to the developmental economy of the individual. One month of constitutional retardation during a period of two months' time in a child's life, guarantees to the individual spiritual inferiority."

Hoepfner<sup>68</sup> showed that in a group of schools of varying rank, the higher the school the higher the percentage of superior capillaries and that the lower the school rank, the higher the percentage of inferior capillaries.

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67. Gesell, A.: Monthly Increments of Development in Infancy, *Pedagog. Sem. & J. Genet. Psychol.* **203**:32, 1925.

Jaensch and his co-workers were of the opinion that close observation of the capillaries in early childhood should be a state measure, as vaccination is, and is of comparative importance to the fighting of infectious diseases. In this instance, we are concerned with the crippling of human beings with mental inferiority and "moral insanity."

So much importance has been attached to this work that the government of Meresburg in Germany has prepared a questionnaire for use in its school system, regarding the psychophysical condition, past history, family history and capillary findings of the school children.

The conception of "vasoneurosis capillaries" is an important contribution of the Tübingen Clinic under the guidance of O. Müller.<sup>68</sup> Certain neurasthenic persons are commonly recognized by their abnormal pallidity or redness of the skin, frequent changes of the color of the skin, easy and quick irritation of the skin after mechanical irritation, acrocyanosis and similar conditions. These vasoneurotic persons are inclined to urticarial states and bleeding, i. e., small hemorrhages of the skin, vicarious menstrual bleeding, intestinal oozing and frequent epistaxis. Many neurasthenic persons do not fall into this group.

The capillaries of some of these vasoneurotic persons exhibit strange and fantastic forms with many intracapillary anastomoses. Observing the flow, one sees stasis, rapidity and frequent intermittency. All of this points to a change in the tonicity of the vascular system, caused by a disorder of interplay between the vagus and the sympatheticus, which leads to an irregular blood supply of the tissues.

Griffith<sup>69</sup> found an occurrence of these grotesque capillary forms in eight of five hundred cases in which there was no evidence of organic peripheral vascular lesions. In thirty-one of five hundred cases the diagnosis was functional neurasthenia. The eight cases in which vasoneurotic capillaries were shown were included in the thirty-one cases of neurasthenia.

Jaensch<sup>70</sup> showed the close relationship between these vasoneurotic capillaries and those showing retarded development as seen in cretinism and other psychopathic states.

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68. Müller, Otfried: *Die Kapillaren der menschlichen Körperoberfläche in gesunden und kranken Tagen*, Stuttgart, Ferdinand Enke, 1922; *Die Naturwissenschaft*, Berlin, Julius Springer, 1929; *Ueber den praktischen Wert der Kapillarpathologie*, Deutsche med. Wchnschr. **56**:574 (April 4) 1930, Parrisius, W.: *Kapillarstudien Vasoneurose*, Deutsche Ztschr. f. Nervenhe. **72**:310, 1921

69. Griffith, J. Q., Jr.: *The Frequent Occurrence of Abnormal Cutaneous Capillaries in Constitutional Neurasthenic States*, Am. J. M. Sc. **183**:180, 1932.

70. Jaensch, W., in Brugsch and Lewy: *Die Biologie der Person*, Berlin, Urban & Schwarzenberg, 1931, vol. 2, p. 954.



Retarded development of the capillaries is also to be noted in cases of mongolian idiocy. Leader<sup>71</sup> found more marked evidence of retardation and pathologic status of the capillaries as the intelligence and physical development were more markedly subnormal.

Powdermaker<sup>72</sup> claimed that children with deficient physical development accompanied by arrested mental development showed pathologically developed capillaries, while Leader<sup>71</sup> found that eighteen children with delayed physical development but normal or superior intelligence showed normal capillaries.

In a study of capillary circulation in the affected psychoses, Sheveleff<sup>73</sup> observed that in depressions the extremities were moist, cold and cyanotic. The capillaries were easily seen. The loops were thickened and widened. Definite retardation in the rate of flow and frequent aneurysms were noted. There was some evidence of diapedesis. Giant loops were seen.

In cases of mania there was no stasis of blood. The extremities were normal in color. The capillaries were not elongated and no aneurysms were seen.

Studies were made by the injection of methylene blue (methylthionine chloride, U.S.P.) into the field of microscopic vision. In normal persons the dye disappeared in two hours. In persons suffering from depressions it took six hours to disappear, while in patients with mania it disappeared in one and one-half hours.

The effects of pilocarpine and epinephrine intradermally injected were also studied. If the capillaries were dilated, pilocarpine produced no effect, but epinephrine produced a marked vasoconstriction with improvement in circulation. Atropine would act in the same manner. When the capillaries were constricted, epinephrine gave no results, but pilocarpine would produce dilatation of the capillaries with the formation of aneurysms. This would last from twenty to sixty minutes. Sheveleff gained the impression that the capillary picture is different in various types of affective psychoses.

*Permeability of the Capillaries in Nervous Disorders.*—Chasanow<sup>31</sup> made a study of the permeability of skin capillaries in nervous disorders. In twenty-three (75 per cent) of thirty cases of epidemic encephalitis, the permeability index was increased. The blister time was prolonged in twenty-one of twenty-six cases (80 per cent) to from ten to fourteen hours. The permeability index was considerably

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71. Leader, S. D.: Capillary Microscopy in Children, *Am. J. Dis. Child.* **44**: 403 (Aug.) 1932.

72. Powdermaker, F.: Capillary Forms in Relation to Certain Problems in Development, *Arch. Neurol. & Psychiat.* **22**:1207 (Dec.) 1929.

73. Sheveleff, N. A.: A Study of Capillary Circulation in the Affective Psychoses, *Zhur. Neuropatol. i Psychiat.* **8**:53, 1931.

increased in eight (80 per cent) of ten cases of multiple sclerosis. The blister time was prolonged to an average of twelve hours for all.

*Mesodermal Syphilis.*—In five of eight cases of mesodermal syphilis the permeability index was normal, but it was considerably increased in three cases in which there were manifestations of meningitis. The blister time was prolonged in seven of these cases to from ten to twelve hours. In *tabes dorsalis*, it was shortened to from five to six hours. In the ectodermal form, the permeability index was increased in three of four cases (75 per cent).

*Diseases of the Vessels of the Central Nervous System.*—The permeability index was increased in seven cases of this type (all acute)

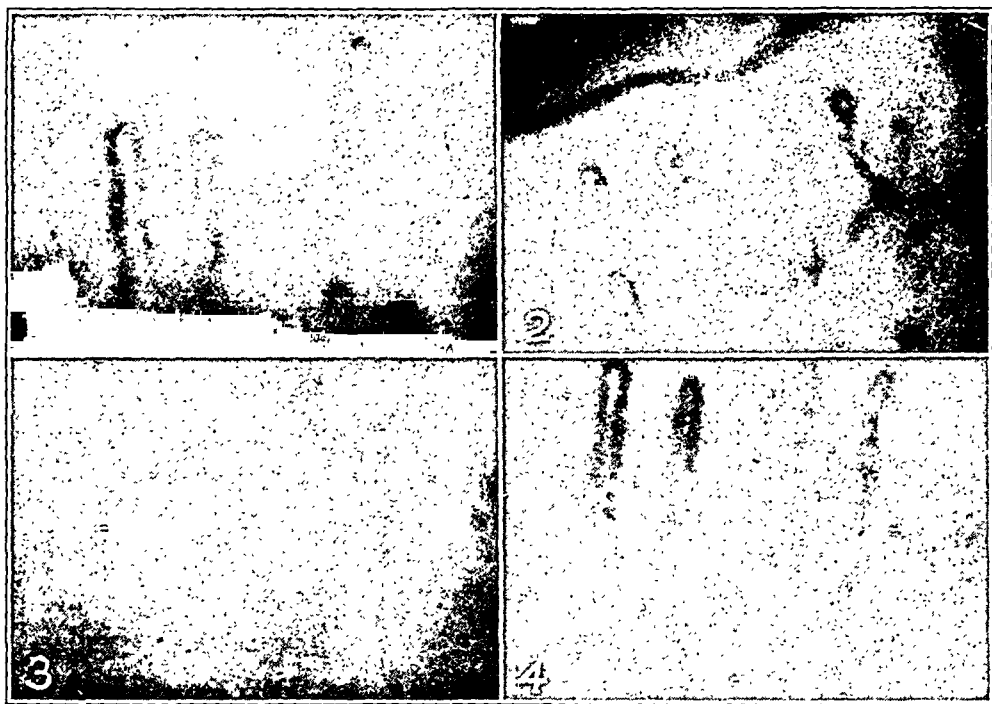


Fig. 14.—Capillaries from four persons with marked clubbing of the fingers. The case of relative polycythemia (fig. 10) offers further variation in this condition. These five cases show the great differences in appearance, number in action, visibility and stoppage which forced us to conclude that there was no definite connection between circulation of the blood and clubbing of the fingers. The primary factors were as follows: 1, congenital heart disease; 2, chronic pulmonary osteoarthropathy; 3, plexiform epithelioma of left main bronchus; 4, splenectomy thirteen years before (relation?).

and normal or decreased in two cases (chronic), 80 per cent. Blister time was prolonged to from ten to twelve hours.

*Diseases of the Peripheral Nerves.*—The permeability index was normal or decreased in chronic cases and increased in acute cases. The blister time was nearly normal in the chronic cases but always prolonged in the acute cases.

*Tumors of the Central Nervous System.*—The permeability index was subnormal in all but two cases of tumor of the central nervous system, and in these two it was above normal. The blister time was prolonged in all of the cases, giving a low inflammation index.

*Clubbing of the Fingers.*—A relationship of the circulation of the blood to clubbing of the fingers and toes has long been an accepted theory. Duken<sup>74</sup> claimed that a definite capillary pattern exists in cases of clubbing due to chronic pulmonary disease. He described the vessels as long, tortuous, spastic, but as a whole dilated. He stated that there was an increase in number with a granular flow but no stasis. Leader<sup>71</sup> claimed that a definite capillary picture develops in the pre-clubbing stage if clubbing is going to develop, so that it is possible to prognosticate in this regard. His cases were all in children and included conditions diagnosed as bronchiectasis, pulmonary abscess and chronic cardiac disease.

One of us (Wright<sup>75</sup>) recently presented the results of a similar study in adults. The cases included examples of congenital cardiac disease, abscess of the lung, tumors of the lung of bronchiogenic, endothelial and unknown origin and chronic pulmonary osteo-arthritis. All the patients had marked clubbing of the fingers. Those with congenital cardiac disease uniformly presented markedly dilated capillaries packed with cells and showing a sluggish flow. Some of these showed increased tortuosity; others did not.

In the other groups there were no uniform findings whatever. Some of those who had the most advanced clubbing of the fingers showed normal capillary pictures, and all variations of rate of flow, tortuosity, size and adult types were found. The fact that clubbing may accompany congestion of the capillaries in congenital cardiac disease and in some other diseases cannot lead to the inference that capillary changes are responsible for clubbing or vice versa, but only that they are coincidental findings. As greatly congested, stagnant capillaries may be present in nail folds of patients for years without the development of clubbing of the fingers, and as the nail fold capillaries of many patients with advanced clubbing of the fingers appear normal in all respects, serious doubt may be entertained as to any definite relationship between these two conditions. Other explanations for clubbing of the fingers, such as disturbance in the lymph drainage, changes in local or general metabolism or the presence of toxic products, are thus far also without scientific proof.

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74. Duken, J.: Das Krankheitsbild der Broncheitektasie im Kindesalter, *Ergebn. d. inn. Med. u. Kinderh.* **34**:457, 1928.

75. Wright, I. S.: Some Observations of Human Capillaries, presented before Section of Medicine, New York Academy of Medicine, March, 1932.

## SUMMARY

An endeavor has been made to review present knowledge concerning human capillaries in health and in many specific diseases. Where our experience has justified, we have added our findings or criticized the findings of others. The field is relatively undeveloped, and it may be expected that present theories will be discarded in the near future, and that many additional pathologic processes will be studied from the point of view of the capillary circulation. No discussion of capillary changes in diseases of the skin has been undertaken, since that subject is vast in itself and has been little studied to date. We have also avoided a detailed discussion of capillary reactions to stimuli. Studies in this field are being undertaken and will be reported at a later date.

# MONOSODIUM THYROXINE, DESICCATED THYROID AND AN IMPURE SODIUM SALT OF THYROXINE

COMPARISON OF THEIR EFFECTS WHEN ADMINISTERED ORALLY  
WITH THE EFFECT OF THYROXINE INJECTED INTRAVE-  
NOUSLY IN AN ALKALINE SOLUTION

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In 1926 we gave some Squibb's thyroxine for oral use to two patients with low basal metabolism for a few days in doses of from 2 to 10 mg. daily and, having observed no effect, were content to conclude that the current opinion about its lack of effect when administered by mouth was correct. However, as time went on, it seemed worth while to give the matter more serious study.

A review of the literature reveals some difference of opinion as to whether or not thyroxine is effective when administered by mouth. Swingle, Helff and Zwemer,<sup>1</sup> by observing the weight and pulse rate, Burmeister,<sup>2</sup> by observing the weight and urinary output, and Abelin,<sup>3</sup> Schneider,<sup>4</sup> and Boller and Högler<sup>5</sup> (Schering's thyroxine), on the basis of determinations of basal metabolism, concluded that thyroxine is virtually without effect when administered by mouth to normal human beings. Weiss<sup>6</sup> observed no effect in some cases of obesity, although in others it appeared to affect the weight slightly. These observers

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From the Department of Medicine, Rush Medical College and the Presbyterian Hospital.

1. Swingle, W. W.; Helff, O. M., and Zwemer, R. L.: The Effect of Thyroxin and Its Acetyl Derivative on Amphibians and Mammals, *Am. J. Physiol.* **70**:208, 1924.

2. Burmeister, E. A.: Klinischer Beitrag zur Thyroxinfrage, *München. med. Wchnschr.* **75**:1073, 1928.

3. Abelin, I.: Zur Kenntnis der Thyroxinbestandteile der Schilddrüse, *München. med. Wchnschr.* **75**:685, 1928.

4. Schneider, E. A.: Ueber die Thyroxinwirkung, *Deutsche med. Wchnschr.* **54**:1561, 1928.

5. Boller, R., and Högler, F.: Klinische Erfahrungen mit Thyroxin, Thyropurin and Thyreoidin, *Klin. Wchnschr.* **8**:1297, 1929.

6. Weiss, R. F.: Bedeutet die Einführung des synthetischen Thyroxins in die Schilddrüsenbehandlung der Fettsucht einen Fortschritt? *Deutsche med. Wchnschr.* **54**:2056, 1928.

apparently used a sodium salt of thyroxine, except Swingle, Helff and Zwemer, who used pure thyroxine also. Gaddum<sup>7</sup> reported pure *l*-thyroxine to be without effect on the oxygen consumption of the rat when given by mouth.

On the other hand, there have been reports that thyroxine has some effect when it is administered by mouth. Plummer,<sup>8</sup> Boothby, Sandiford, Sandiford and Slosse,<sup>9</sup> Schittenhelm and Eisler,<sup>10</sup> Knipping,<sup>11</sup> Zondek and Köhler,<sup>12</sup> Aschner,<sup>13</sup> and Klein<sup>14</sup> observed some effect on the basal metabolism in patients with myxedema, and Snell, Ford and Rowntree<sup>15</sup> and Fonio and Scheurer<sup>16</sup> observed some effect in cretins. Some effect on the oxygen consumption in normal human beings was observed by Grawitz and Dubberstein,<sup>17</sup> Baur and Loewe,<sup>18</sup> Auerbach and Klein,<sup>19</sup> Boller and Höglér<sup>5</sup> (one case with Henning's thyroxine) and Klein.<sup>14</sup> Some effect on the basal metabolism in obesity was

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7. Gaddum, J. H.: Quantitative Observations on Thyroxine and Allied Substances: II. Effects on the Oxygen Consumption of Rats, *J. Physiol.* **68**:383, 1930.

8. Plummer, H. S.: Interrelationship of Function of the Thyroid Gland and of Its Active Agent, Thyroxin, in the Tissues of the Body, *J. A. M. A.* **77**:243 (July 23) 1921.

9. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects: I. A Method of Studying the Reserve or Deposit Protein with a Preliminary Report of the Results Obtained, *Ergebn. d. Physiol.* **24**: 728, 1925.

10. Schittenhelm, A., and Eisler, B.: Ueber die Wirksamkeit des Thyroxins (Schering) bei Endokrin bedingten Störungen, *Klin. Wchnschr.* **6**:1935, 1927.

11. Knipping, H. W.: Ergebnisse der Gasstoffwechseluntersuchung für die Klinik, *Klin. Wchnschr.* **7**:49, 1928.

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13. Aschner, B.: Ueber Thyroxintherapie und ihre Indikationen, *Ztschr. f. klin. Med.* **114**:360, 1930.

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15. Snell, A. M.; Ford, F., and Rowntree, L. G.: Studies in Basal Metabolism, *J. A. M. A.* **75**:515 (Aug. 15) 1920.

16. Fonio, A., and Scheurer, G.: Ueber die Wirkung des Thyroxins und des Jodes in einer dem Jodgehalt des Thyroxins entsprechenden Dosierung auf einige Abschnitte des Stoffwechsels, auf das Blut usw. bei endemischen Kretinen, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **42**:467, 1931.

17. Grawitz, E. R., and Dubberstein, W.: Klinische Prüfung des synthetischen Thyroxin-Henning, *Klin. Wchnschr.* **7**:797, 1928.

18. Baur, H., and Loewe, G.: Ueber die Wirkung des synthetischen Thyroxins beim Menschen mit normaler Schilddrüse, *Deutsches Arch. f. klin. Med.* **159**:275, 1928.

19. Auerbach, L., and Klein, B.: Vergleichende Untersuchungen über die Wirksamkeit synthetischer Schilddrüsenpräparate, *Klin. Wchnschr.* **8**:2332, 1929.

observed by Weiss<sup>6</sup> and Hellfors;<sup>20</sup> some effect on the weight in obesity, by Zondek and Köhler;<sup>12</sup> some effect on the oxygen consumption of rats, by Abelin;<sup>3</sup> and some effect on the oxygen consumption of one dog, by Kunde.<sup>21</sup> Hunt<sup>22</sup> noted that it protected white mice against acetonitrile, and Cameron and Carmichael,<sup>23</sup> that it produced some reduction in the growth rate of rats, as well as hypertrophy of the heart, liver, kidneys and suprarenals and decrease of the growth rate of the thyroid. Lipschitz and Girndt<sup>24</sup> and Krogh and Lindberg<sup>25</sup> showed that it reduced the weight of guinea-pigs.

A few quantitative observations have been reported. In 1921, Plummer<sup>8</sup> reported that "a daily oral dose of 1.6 mg. of thyroxin [1.1 mg. of iodine] will hold the basal metabolism of most thyroidless individuals within normal limits." In contrast with this, the maintenance dose of desiccated thyroid was 130 mg., an amount which contained about 0.26 mg. of iodine. In 1924, Plummer and Boothby<sup>26</sup> made the statement that "desiccated thyroid has been found to be absorbed from the gastro-intestinal tract with greater regularity than has the impure sodium salt of thyroxin. In fact, the absorption of the latter in persons with low basal metabolic rates which we do not attribute to myxedema is very erratic." Boothby, Sandiford, Sandiford and Slosse<sup>9</sup> concluded that 1.6 mg. daily of an impure sodium salt held the basal metabolism of a thyroidless person (basal metabolism, minus 40 per cent) at a level of about zero and 0.8 mg. daily at a level of minus 15 per cent. The dose of 1.6 mg. daily was administered for thirteen days and the dose of 0.8 mg. for twenty-one days after the basal metabolism had been raised to normal by two intravenous injections of thyroxine of 7 mg. each. Kunde<sup>21</sup> gave a dog from 4 to 15 mg. of Kendall's pure crystalline thyroxine daily for eighty-one days and noted a maximum increase of basal metabolism of 119 per cent on the seventieth day. Schittenhelm and Eisler,<sup>10</sup> using Schering's thy-

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20. Hellfors, A.: Beitrag zur systematischen Entfettungskur mittels Thyroxin, München. med. Wchnschr. **78**:826, 1931.

21. Kunde, M. M.: Studies on Metabolism: VI. Experimental Hyperthyroidism, Am. J. Physiol. **82**:195, 1927.

22. Hunt, R.: The Acetonitril Test for Thyroid and Some Alterations of Metabolism, Am. J. Physiol. **63**:257, 1923.

23. Cameron, A. T., and Carmichael, J.: Contributions to the Biochemistry of Iodine: IV. The Effect of Thyroxin on Growth in White Rats and in Rabbits, J. Biol. Chem. **46**:35, 1921.

24. Lipschitz, W., and Girndt, O.: Wertbestimmung von Schilddrüsenpräparaten des Handels, Arch. f. exper. Path. u. Pharmakol. **159**:259, 1931.

25. Krogh, M., and Lindberg, A. L.: Studies on the Thyroid Gland: II. The Physiological Activity of Iodine in Thyroxin and in Normal and Pathological Thyroid Glands, Acta path. et microbiol. Scandinav. **9**:21, 1932.

26. Plummer, H. S., and Boothby, W. M.: Glandular Therapy: Administration of Thyroid Preparations, J. A. M. A. **83**:1333 (Oct. 25) 1924.

roxine, noted greater effect in a case of myxedema from 12 mg. of thyroxine intravenously than from 45 mg. by mouth, and in another case, about the same effect from 84 mg. by mouth as from 16 mg. intravenously. All quantities recorded were given in divided doses over a short period, and tablets were used for oral administration. Grawitz and Dubberstein<sup>17</sup> produced an increase in basal metabolism of from 27 (minus 13 to plus 14 per cent) to 48 (minus 35 to plus 13 per cent) points in four patients by administering Henning's thyroxine tablets in doses which varied from 18.5 mg. in two weeks to 57 mg. in four weeks. They concluded that 1 mg. of thyroxine was the equivalent of 0.2 Gm. of thyreoidin. Schneider<sup>4</sup> noted that the metabolism rose from zero to plus 20 per cent during the administration of thyroxine to nine patients, in doses varying from 14 mg. in seven days to 72 mg. in fourteen days. He concluded that the oral administration of 2 mg. daily produced an uncertain and transient rise.

Zondek and Köhler<sup>12</sup> apparently held the basal metabolism of one patient with myxedema at the normal level by administering 1 mg. of synthetic thyroxine (Roche) daily by mouth after the basal metabolism had been raised to normal by giving thyroxine intravenously, whereas in another patient with myxedema the basal metabolism dropped while she was receiving 2 mg. daily by mouth. In obese patients a marked loss in weight occurred while from 8 to 10 mg. was being administered daily. Weiss<sup>6</sup> used from 6 to 8 mg. of Roche's synthetic thyroxine daily in the treatment of obesity and thought it produced less toxic effects than thyreoidin. In some cases of obesity that were refractory to treatment with thyroid, he found that from 0.6 to 0.8 Gm. of thyreoidin Merck daily was effective when from 10 to 12 mg. of thyroxine was actionless. Baur and Loewe<sup>18</sup> came to the conclusion that synthetic thyroxine (Roche) subcutaneously or by mouth in human beings with normal thyroid function had the same action as approximately one hundred times that amount of dried thyroid. Auerbach and Klein<sup>19</sup> concluded that Roche's synthetic thyroxine had only about one-half as much effect when given by mouth as when given intravenously. Harington and Salter,<sup>27</sup> in their paper on the isolation of a polypeptide of thyroxine by tryptic digestion, reported that Gaddum found that "the oral administration of 1 mg. *per diem* for 6 days of pure *l*-thyroxine had practically no effect on the oxygen consumption of a rat, whilst an equivalent dose of the digestion product (1.3 mg. *per diem* for 6 days of a preparation containing 50 per cent of iodine) produced an increase in the oxygen consumption of 85 per cent. By the subcutaneous route, on the other hand, single doses of 1 mg. of *l*-thyroxine and

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27. Harington, C. R., and Salter, W. T.: The Isolation of *l*-Thyroxine from the Thyroid Gland by the Action of Proteolytic Enzymes, *Biochem. J.* **24**:456, 1930.



1.3 mg. of the digestion product caused increases in the oxygen consumption of 32.5 per cent and 37.5 per cent respectively. . . .” Hellfors,<sup>20</sup> by giving comparatively large doses of thyroxine in a short time (e. g., 41.5 mg. in seventeen days) to obese patients, concluded that 0.5 mg. of thyroxine Henning raised the basal metabolism 2 per cent; 2 mg. of thyroxine Schering, 1 per cent; 1 mg. of synthetic thyroxine (Roche), 1 per cent, and one tablet of thyreoidin Merck (0.1 Gm.), from 1 to 3 per cent. Klein<sup>14</sup> recommended that in the treatment of myxedema from 3 to 4 mg. daily be used for the first two or three weeks and then from 1 to 2 mg. daily. In one patient, she produced an increase in the basal metabolism from minus 12 per cent to plus 10 per cent by administering 222 mg. of thyroxine (Schering's tablets) in thirty-seven days; in a second patient, an increase from minus 14 per cent to plus 19 per cent by administering 138 mg. in twenty-six days; in a third patient, an increase from plus 8 to plus 28 per cent by administering 75 mg. in sixteen days; in a fourth patient, an increase from plus 1 to plus 16 per cent by administering 72 mg. in twelve days, and in a fifth patient, an increase from minus 4 to plus 10 per cent by administering 30 mg. in five days. Greater effects were obtained by giving Hoffmann-La Roche's alkaline solution for oral administration, Schering's thyroxine in alkaline solution and Schering's tablets, which are said to contain dialkali salts of thyroxine. Indeed, Klein concluded that thyroxine when given in suitable form and dose has the same effect orally as parenterally. Baur and Loewe<sup>18</sup> likewise concluded that it was more effective by mouth if given in alkaline solution, especially if the solution was markedly diluted.

The observations reported create the impression that thyroxine is effective by mouth when given in tablet form, but is less effective than when given intravenously in alkaline solution. However, there are no adequate data for comparing their effects quantitatively by these two methods of administration. One of the chief difficulties with the data already reported is that the effect by a given route has been observed over too short a period. Our data suggest that it is sometimes necessary to wait several months before the metabolism reaches a level during the administration of a given dose. Moreover, the precise form in which thyroxine was administered was not stated in most instances. Gaddum<sup>7</sup> used pure *l*-thyroxine. Kunde<sup>21</sup> used the pure crystalline thyroxine of Kendall. Plummer and Boothby<sup>26</sup> used an impure sodium salt of thyroxine which represented the acid-insoluble fraction after the preliminary hydrolysis with sodium hydroxide in the separation of thyroxine from the thyroid gland. Because of variations that may result in a product obtained by approximately the same chemical procedure, Plummer<sup>28</sup> does not feel sure that this is the same

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28. Plummer, H. S.: Personal communication.

as the impure sodium salt which Squibb now manufactures for oral use. Most other observers refer to the absorption of thyroxine, but an investigation of the products which they used (the thyroxine tablets of Henning, Schering and Hoffmann-La Roche) shows that they did not contain pure thyroxine but a sodium salt of thyroxine. A perusal of the data reported in this and subsequent papers will show this distinction to be of importance.

The present study has two objectives:

1. To prove definitely whether or not thyroxine is effective when administered by mouth.
2. A quantitative comparison of the effects of administering thyroxine by the oral and parenteral routes and desiccated thyroid by mouth.

#### METHOD

All of our observations have been made on patients with myxedema; in other words, in conditions under which all thyroid preparations are known to have their greatest effect. To exclude the possibility of variations in effect from patient to patient, the various preparations used have been compared in the same patient. We have determined the effect of various doses of Squibb's crystalline thyroxine when administered intravenously or subcutaneously; the effect of various doses of the monosodium salt of synthetic thyroxine (Hoffmann-La Roche) by mouth, and the effect of various doses of Wilson's desiccated thyroid (iodine content, 0.23 per cent) by mouth. There are also some data on the effect of oral administration of pure synthetic thyroxine and Squibb's thyroxine tablets for oral use. More data on the effect of these two substances will be reported at a later date. The pure synthetic thyroxine used for oral administration was given in the form of tablets containing 1 mg. each, which were specially prepared for us by Hoffmann-La Roche. The monosodium salt of thyroxine refers to the so-called thyroxine tablets which Hoffmann-La Roche ordinarily sell for oral administration. Each tablet contains 1.03 mg. of the monosodium salt and hence is equivalent to 1 mg. of thyroxine. The Squibb thyroxine for oral use is said by the manufacturers to be the acid-insoluble fraction after the preliminary alkaline hydrolysis in the separation of thyroxine from the thyroid gland and was used in the form of tablets containing 0.4 mg. each. Its exact composition is apparently not known. According to "New and Nonofficial Remedies,"<sup>29</sup> it is the partially purified disodium salt of thyroxine, approximately 25 per cent admixed with the acid-insoluble humus-like products of protein hydrolysis. The tablets that we received from Squibb during the latter part of our observations were slightly darker than those we received during the first part. Whether variations in composition account for some of the variations in effect in the different patients is uncertain. Although synthetic thyroxine was used by mouth and Squibb's thyroxine intravenously, both appear to be the same thing chemically and physiologically.

The data on the first patient up to the five hundred and eighth day and on the second patient up to the four hundred and fifteenth day have been reported else-

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29. New and Nonofficial Remedies, Chicago, American Medical Association, 1931.

where to illustrate another point (Thompson, McLellan, Thompson and Dickie<sup>30</sup>). The method of preparing the thyroxine (Squibb) for intravenous and subcutaneous injection may be seen in that report. All that seems of importance in the present paper is to state that it was put into solution for injection by adding to its suspension in distilled water 2 or 3 drops of 10 per cent sodium hydroxide.

TABLE 1.—Effect on Basal Metabolism of the Daily Administration of Thyroxine in Various Forms and of Desiccated Thyroid in Six Patients with Myxedema

Form	Daily Medication		Basal Metabolic Rate, per Cent Normal					
	Amount, Mg.	Method of Administration	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
None .....	....	.....	—33	—41	—34	—31	—25	—18
Squibb's crystalline thyroxine in alkaline solution	0.05	Intravenously	....	—34				
	0.10	Intravenously	—21	—25				
	0.20	Intravenously	—7	—15				
	0.30	Intravenously	+ 1	—8				
	0.40	Intravenously or subcutaneously	....	+ 5				
Squibb's tablets (impure sodium salt of thyroxine)	0.20	By mouth	—12	—12	—12			
	0.40	By mouth	—4	....	—7	—4		
	0.60	By mouth	—8	—1	—6			
Hoffmann-La Roche's tablets (monosodium salt of synthetic thyroxine)	1.03	By mouth	....	....	....	—10	+ 8	+27
	1.55	By mouth	+ 7	+ 6	+ 2	+ 6		
	2.06	By mouth	+23	+ 9	+ 5			
Hoffmann-La Roche's tablets (pure synthetic thyroxine)	1.00	By mouth	—19	—13	—24			
	2.00	By mouth	....	—12				
Wilson's desiccated thyroid	0.86 grain	By mouth	....	....	....	....	....	+ 2
	1 grain	By mouth	—6	—16				
	1.5 grain	By mouth	+ 7	+ 1				

TABLE 2.—Comparison of the Doses of the Various Substances Required to Hold the Basal Metabolism at the Normal Level, on the Basis of Their Iodine Contents

Form	Iodine Content of Maintenance Dose (Mg.)					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Wilson's desiccated thyroid by mouth.....	0.19	0.23	....	....	....	0.12
Squibb's crystalline thyroxine intravenously in alkaline solution.....	0.20	0.23				
Squibb's tablets (impure sodium salt of thyroxine) by mouth.....	0.46	0.40	0.47	0.30		
Hoffmann-La Roche's tablets (monosodium salt of synthetic thyroxine) by mouth	0.85	0.88	0.94	0.82	0.49	0.26

There are three methods of comparing the substances used in patients with myxedema:

1. Determination of the dose that is just adequate to maintain the basal metabolism at the normal level.

30. Thompson, W. O.; McLellan, L. L.; Thompson, P. K., and Dickie, L. F. N.: The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man: Relation Between the Iodine in Desiccated Thyroid and in Thyroxine, J. Clin. Investigation 12:235, 1933.

2. Determination of the effect on the basal metabolism of a single large dose, e.g., 10 mg. of thyroxine or its equivalent.

3. Determination of the rate at which a given dose will raise the basal metabolism to normal.

For the purposes of the present study we have selected the first method.

#### DATA

The data are summarized in tables 1 and 2 and recorded in detail in charts 1 to 7. The level recorded on any dose of any preparation is the average of the basal metabolisms after the rate had become stationary during the administration of the particular dose. It may be noted that the dose of any substance was rarely changed until the patient had been receiving it for several months.

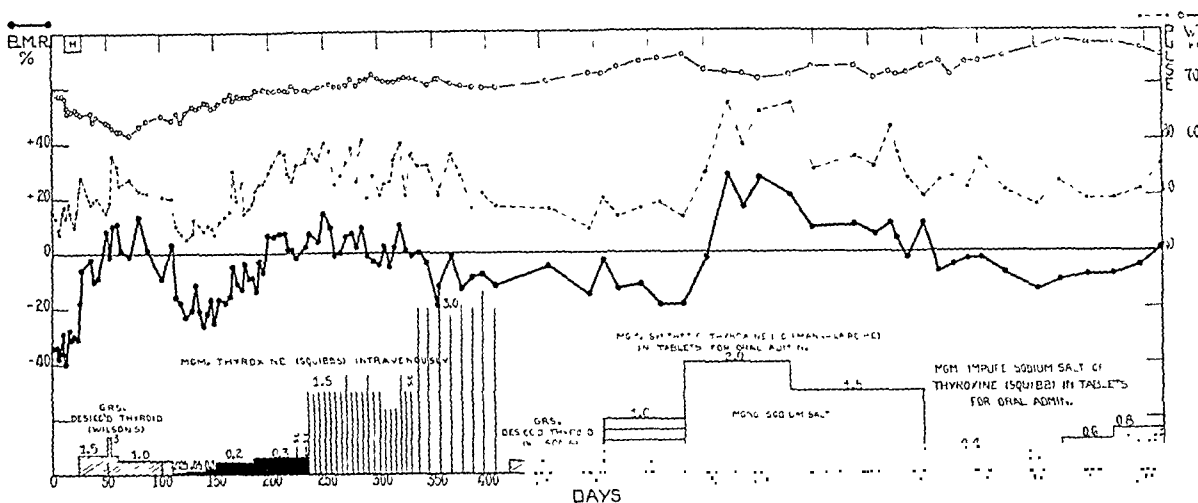


Chart 1.—Comparison of the effects of administering various forms of thyroxine by mouth, desiccated thyroid by mouth and thyroxine intravenously in a patient with myxedema (Miss M. F.; height, 161 cm.; age, 42).

In this and subsequent charts the solid black line represents the basal metabolic rate; the broken line, the pulse rate and the line of circles, the weight.

In the first patient (chart 1), whose basal metabolism was minus 33 per cent during the myxedematous state, the rate could be held at the normal level in the following ways:

1. By the daily administration of 0.3 mg. of Squibb's crystalline thyroxine intravenously (0.2 mg. of iodine).

2. By the daily administration of about 1.25 grains (81 mg.) of Wilson's desiccated thyroid (0.19 mg. of iodine). (For the calculation of this and the first figure, see a previous report by Thompson, McLellan, Thompson and Dickie.<sup>30</sup>).

3. By the daily oral administration of about 1.3 mg. of the monosodium salt of thyroxine (0.85 mg. of iodine). (This was calculated from the fact that 1.55 mg. daily held the basal metabolism at a level of plus 7 per cent.)

4. By the daily administration of about 0.71 mg. of Squibb's thyroxine (0.46 mg. of iodine) for oral use (calculated from the fact that 0.6 mg. daily held the basal metabolism at a level of minus 8 per cent).

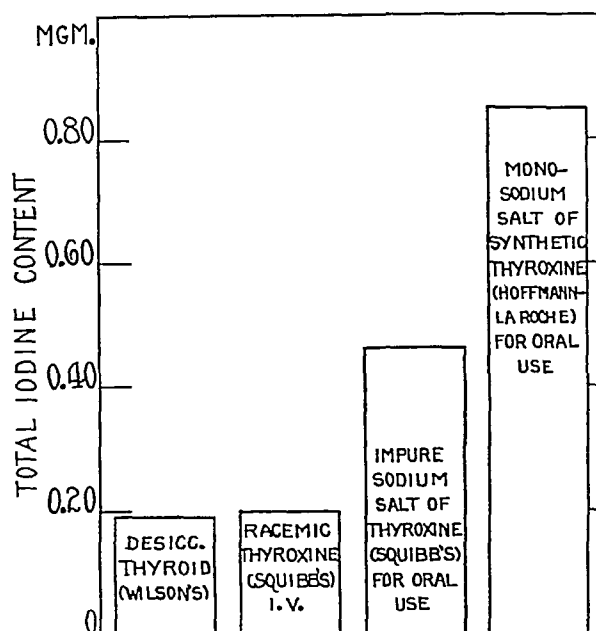


Chart 2.—Comparison of the amounts of iodine in the doses of the various substances necessary to hold the basal metabolism at the normal level in the first patient.

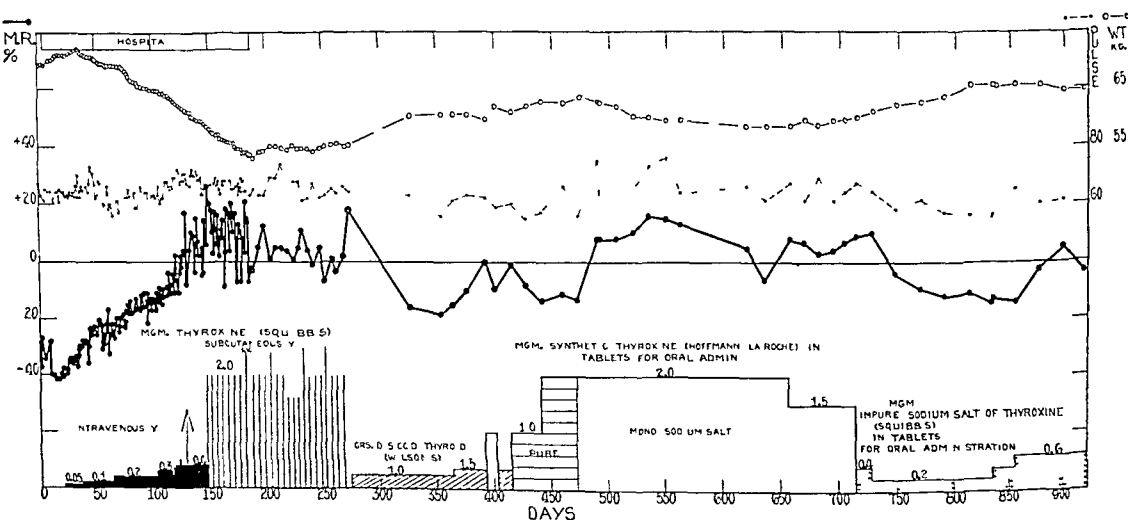


Chart 3.—Comparison of the effects of administering various forms of thyroxine by mouth, desiccated thyroid by mouth and thyroxine intravenously and subcutaneously in a patient with myxedema (Mrs. M. R.; height, 155 cm.; age, 40).

In chart 2 we have compared the daily maintenance dose of the four substances mentioned on the basis of their iodine contents.

In the second patient (chart 3), whose basal metabolism was minus 41 per cent during the myxedematous state, the rate could be held at the normal level in the following ways:

1. By the daily intravenous or subcutaneous administration of about 0.35 mg. of Squibb's crystalline thyroxine (iodine content, 0.23 mg.).

2. By the daily administration of about 1.5 grains (97 mg.) of Wilson's desiccated thyroid (0.23 mg. of iodine). (For the calculation of these first two figures, see a previous paper by Thompson, McLellan, Thompson and Dickie.<sup>30</sup>)

3. By the daily oral administration of about 1.35 mg. of the monosodium salt of thyroxine (0.88 mg. of iodine). (This was calculated from the fact that 1.55 mg. daily held the basal metabolism at a level of plus 6 per cent.)

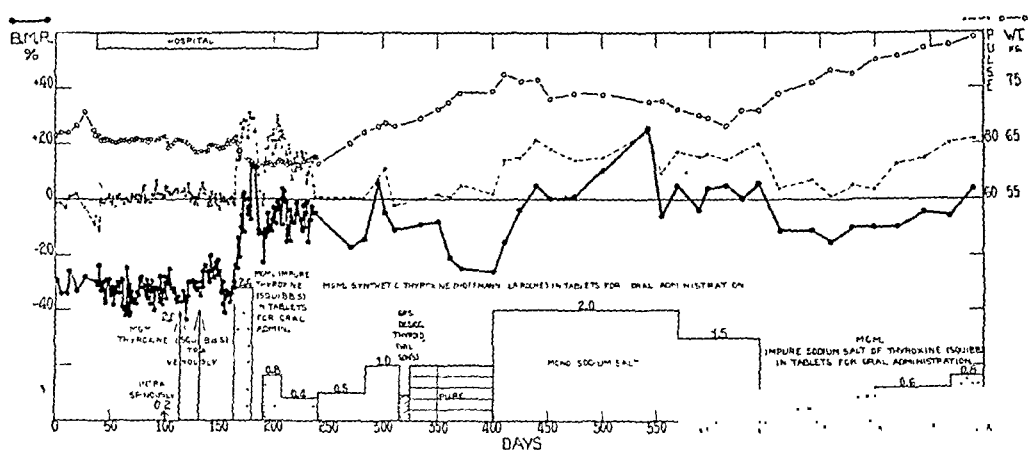


Chart 4.—Comparison of the effects of the oral administration of an impure sodium salt of thyroxine and the monosodium salt of synthetic thyroxine in a patient with myxedema (Mrs. E. R.; height, 167.5 cm.; age, 44).

4. By the daily administration of about 0.61 mg. of Squibb's thyroxine (0.4 mg. of iodine) for oral use (calculated from the fact that 0.6 mg. daily held the basal metabolism at a level of about minus 1 per cent).

In the third patient (chart 4), whose basal metabolism was minus 34 per cent during the myxedematous state, the rate could be held at the normal level in the following ways:

1. By the daily administration of about 0.73 mg. of Squibb's thyroxine (iodine content, 0.47 mg.) for oral use (calculated from the fact that 0.6 mg. daily held the basal metabolism at a level of minus 6 per cent).

2. By the daily oral administration of about 1.46 mg. of the monosodium salt of thyroxine (iodine content, 0.94 mg.). (This was calculated from the fact that 1.55 mg. held the basal metabolism at a level of plus 2 per cent.)

In the fourth patient (chart 5), whose basal metabolism was minus 31 per cent during the myxedematous state, the rate could be held at the normal level in the following ways:

1. By the daily administration of about 1.3 mg. of the monosodium salt of thyroxine (0.82 mg. of iodine), judging from the level on 1.55 mg. per day. If, however, the level to which the basal metabolism was raised by 1.03 mg. daily (minus 10 per cent) were used in the calculation, the figure for maintenance at the normal level would be raised to 1.52 mg. daily.

2. By the daily administration of about 0.46 mg. of Squibb's thyroxine (iodine content, 0.3 mg.) for oral use (calculated from the fact that 0.4 mg. daily held the metabolism at a level of minus 4 per cent).

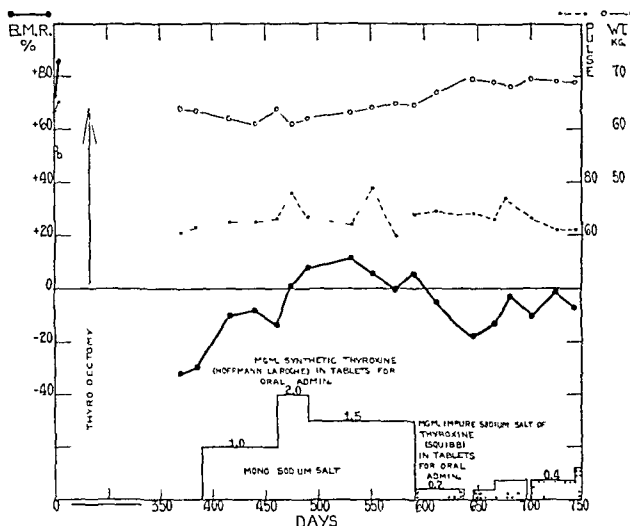


Chart 5.—Comparison of the effects of the oral administration of an impure sodium salt and the monosodium salt of synthetic thyroxine in a patient with myxedema (Miss M. T.; height, 164 cm.; age, 40).

In the fifth patient (chart 6), whose basal metabolism was minus 25 per cent during the period of myxedema, the rate could be held at the normal level by the daily administration of about 0.78 mg. of the monosodium salt (0.49 mg. of iodine), judging from the fact that 1.03 mg. daily held the basal metabolism at a level of plus 8 per cent. Data on this patient during her pregnancy have been ignored in calculating levels.

In the sixth patient (chart 7) whose basal metabolism was minus 18 per cent after the administration of desiccated thyroid had been omitted for eighty-five days, the basal metabolism could be held at the normal level in the following ways:

1. By the administration of about 0.77 grains (50 mg.) of Wilson's desiccated thyroid (0.12 mg. of iodine) daily (calculated from the fact that 0.86 grains (56 mg.) daily held the rate at plus 2 per cent).

2. By the daily administration of about 0.4 mg. (0.26 mg. of iodine) of the monosodium salt of thyroxine (calculated from the fact that 1.03 mg. daily held the metabolism at plus 27 per cent).

It may be noted that in the first and third patients the level during the administration of 1 mg. of Hoffmann-La Roche's synthetic thyroxine daily by mouth was lower than would be expected on the basis of the results with 1.5 mg. daily. Thus, in the first patient, the basal

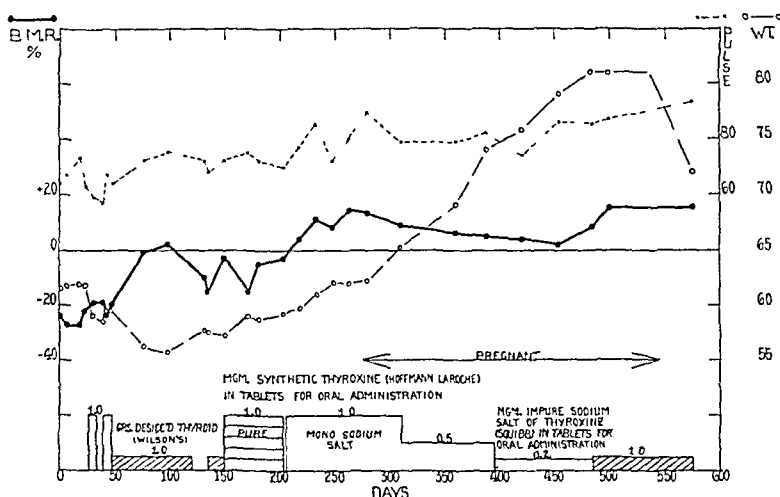


Chart 6.—Effects of the oral administration of monosodium thyroxine in a patient with myxedema (Mrs. M. S.; height, 164 cm.; age, 37).

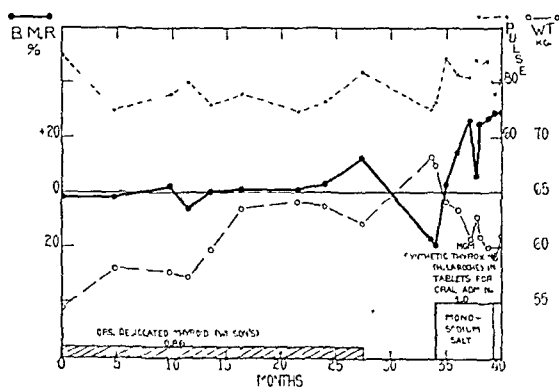


Chart 7.—Comparison of the effects of oral administration of desiccated thyroid and monosodium thyroxine in a cretin (Mr. J. K., age 20). (The height of this patient varied during the period of observation as follows: Jan. 3, 1930, 157.5 cm.; May 26, 1930, 161 cm.; Oct. 24, 1930, 165 cm.; May 16, 1931, 166 cm.; April 2, 1932, 167 cm.; Nov. 19, 1932, 167.5 cm.).

metabolism dropped to minus 19 per cent during the administration of 1 mg. daily, although it was plus 7 per cent during the administration of 1.5 mg. daily; and in the third patient, the corresponding levels were minus 24 and plus 2 per cent, respectively. In the second patient, it may be seen that during the first administration of 2 mg. of Hoffmann-La Roche's synthetic thyroxine daily by mouth, the metabolism dropped to a lower level (minus 12 per cent) than it was later



during the administration of 1.5 mg. daily (plus 6 per cent). In the fifth patient, when the administration of Hoffmann-La Roche's synthetic thyroxine by mouth was first substituted for that of Wilson's desiccated thyroid the metabolism dropped to a level of minus 10 per cent and then later it was at a level of plus 8 per cent on the same dose. We were at a loss to explain these apparent discrepancies until a careful perusal of our data showed that the results which seemed to be too low coincided with the administration of pure crystalline thyroxine in tablet form instead of its monosodium salt. From these data, it would appear that pure crystalline thyroxine may have a slight effect when given by mouth. If they were fair indications of its effect by this route, it would have taken 2.4, 2.8, 3.4 and 1.7 mg. daily, respectively, in patients 1, 2, 3 and 5 in order to hold the basal metabolism at the normal level. This is from two to two and one-half times as much as was required of the monosodium salt to accomplish the same result. However, since these data were collected we have observed that the administration of single doses of from 10 to 100 mg. of pure crystalline thyroxine by mouth or duodenum to patients with myxedema had little or no effect on the basal metabolism. In one patient with marked myxedema we have been able to raise the basal metabolism from minus 40 per cent to normal by the prolonged oral administration of pure thyroxine, first in a dose of 25 mg. daily and then in a dose of 50 mg. daily. The exact amount necessary to maintain the metabolism at the normal level in this patient is yet to be determined.

While thyroxine has much less effect when given orally in the form of its monosodium salt than when given intravenously in alkaline solution, the effect of the monosodium salt was nevertheless not spasmodic but fairly constant in the six cases observed. Thus, in patients 1, 2, 3 and 4, whose levels of basal metabolism during the period of myxedema were minus 33 per cent, minus 41 per cent, minus 34 per cent and minus 31 per cent, respectively, the daily administration of 1.55 mg. held the metabolism at levels of plus 7 per cent, plus 6 per cent, plus 2 per cent and plus 6 per cent, respectively, changes of from 36 to 47 points, or changes per milligram of from 23 to 30 points. In patients 5 and 6, whose levels of basal metabolism during the myxedematous state were minus 25 per cent and minus 18 per cent, respectively, 1.03 mg. daily by mouth held the metabolism at levels of about plus 8 per cent and plus 27 per cent, respectively, or a change per milligram of 32 points in the fifth patient and 44 points in the sixth. Thus, in all six patients the average change per milligram was 30 points, with a maximum change of 44 points and a minimum change of 23 points. Some observations which we have made recently on the effect of single large doses of the monosodium salt by mouth indicate that a greater variation in effect may occur. Thus, in one patient with myx-

edema the administration of 10.3 mg. of the monosodium salt raised the basal metabolism from minus 37 per cent to minus 22 per cent, whereas in another patient with myxedema the administration of 30.9 mg. in one dose raised the metabolism only from minus 22 per cent to minus 12 per cent.

In the first patient it may be noted that when the administration of Squibb's tablets was first substituted for that of the monosodium salt of thyroxine, a dose of 0.4 mg. per day appeared to hold the basal metabolism at a level of about minus 4 per cent for about two and one-half months, whereas later 0.6 mg. per day held the metabolism at a level of only minus 8 per cent. There are at least two possible explanations for these apparent discrepancies:

1. In patients with myxedema the basal metabolism drops slowly from the normal level on omission of medication, and a dose of thyroxine which might be inadequate for maintenance at the normal level over a long period might appear to be adequate for a short period.

2. The composition of Squibb's tablets may vary. The data on the first three patients are consistent with the first explanation. Thus, in the first patient, when the administration of 0.2 mg. daily of Squibb's thyroxine for oral use was substituted for the administration of 0.4 mg. daily for forty-nine days, the basal metabolism dropped to only minus 12 per cent. The data during the daily administration of 0.2 mg. in the second and third patients likewise show a greater response to this small dose than would be expected from the results with larger doses. Slow reduction in metabolism may also explain the fact that pure synthetic thyroxine administered by mouth appeared to have a greater effect in the first three patients and in the fifth patient than we would expect on the basis of our recent data previously referred to.

#### COMMENT

The main problem is why the form in which thyroxine is given by mouth determines its effect on the basal metabolism. To be more specific, the things to be explained are why it has much less effect when administered by mouth in the form of its monosodium salt than when given intravenously or subcutaneously in alkaline solution, and much less effect than when given orally in the form of desiccated thyroid or combined with a polypeptide (Salter, Lerman and Means<sup>31</sup>), and why pure thyroxine itself has even less effect than its monosodium salt when given by mouth. There appear to be at least three explana-

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31. Salter, W. T.; Lerman, J., and Means, J. H.: The Calorigenic Action of Thyroxin Polypeptide, *J. Clin. Investigation* **12**:327, 1933.

tions possible: (1) the solubility of the substance administered, (2) destruction in the gastro-intestinal tract and (3) some undetermined factor.

Knipping<sup>31</sup> favored the second view, and said that since thyroxine has less effect when given by mouth than when given intravenously it must follow that some of it is destroyed in the gastro-intestinal tract. Barnes<sup>32</sup> recently obtained suggestive evidence that thyroxine may be destroyed to the extent of about 11 per cent in vitro by the action of pancreatic enzymes. We<sup>30</sup> have previously reported that in the first two patients of this study, about the same results were obtained with desiccated thyroid by mouth as with thyroxine intravenously on the basis of equal iodine contents, and Salter, Lerman and Means<sup>31</sup> showed that the effect of thyroxine polypeptide is nearly as great when given by mouth as when given intravenously. It would, therefore, seem that if any destruction of thyroxine occurs, it is not very great when the thyroxine is combined with a protein or a polypeptide. It is uncertain how far the digestion of desiccated thyroid or of thyroxine polypeptide proceeds in the small intestine and just in what form thyroxine is absorbed. Barnes, Carlson and Riskin<sup>33</sup> showed that, during the digestion of desiccated thyroid, no iodine compound can be precipitated from the blood with a half-saturated solution of ammonium sulphate. Harington and Salter<sup>27</sup> found a small amount of free thyroxine at the end of from seventy-two to ninety-six hours in the preparation of their thyroxine polypeptide by tryptic digestion of 70 Kg. of dried thyroid.

While destruction in the gastro-intestinal tract is a comparatively simple explanation, we are reasonably certain that at best it accounts for only a part of the differences in effects observed. If it were the only explanation, it would seem strange that the monosodium salt of thyroxine was less affected by intestinal enzymes than thyroxine itself. Moreover, we have just made observations which show that when thyroxine is given by mouth in alkaline solution (disodium salt), it has much more effect than when given in the form of its monosodium salt. Since thyroxine is the least soluble of the three and the disodium salt the most soluble, the solubility of the thyroxine compound administered would appear to be a factor in its absorption. It might be supposed that the alkalinity of the contents of the small intestine would cause some of the sodium salt of thyroxine to be formed. However, it is probable that if this reaction occurs at all, it affects only a small part of the thyroxine, because we have given single doses of as

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32. Barnes, B. O.: Personal communication.

33. Barnes, B. O.; Carlson, A. J., and Riskin, A. M.: Studies on Thyroglobulin: I. The Digestibility of Thyroglobulin, *Am. J. Physiol.* **98**:86, 1931.

much as 50 mg. directly into the duodenum in patients with myxedema without demonstrable effect on the basal metabolism. Harington and Salter<sup>27</sup> said: "The physical properties of thyroxine are such as to make it highly probable that the absorption of this substance after oral administration would be inefficient and erratic; the digestion product, on the other hand, possessing as it does a much wider range of solubility, might well be absorbed almost quantitatively . . ." Solubility of the thyroxine compound administered would, therefore, appear to be important and destruction by intestinal enzymes must be considered; but only future work will determine whether or not some other factor, as yet unknown, also plays a rôle.

Schittenhelm and Eisler<sup>34</sup> made interesting observations which show that the site of absorption of thyroxine is the small intestine and that comparatively little is absorbed from the stomach. However, they used only an alkaline solution of thyroxine, and their experiments, while very instructive in themselves, do not solve the problem discussed here.

The difference in effect between the monosodium salt of thyroxine and Squibb's thyroxine for oral use is of interest. The fact that Squibb's tablets contain some disodium thyroxine may account in part for their greater action.

#### SUMMARY

In six patients with myxedema whose basal metabolism varied from minus 18 per cent to minus 41 per cent (average, minus 30 per cent) during the period of myxedema, it was necessary to administer from 0.40 to 1.46 mg. (average, 1.1 mg.) of the monosodium salt of thyroxine daily by mouth in order to hold the basal metabolism at the normal level. In the two patients in whom a comparison of the daily maintenance dose was made, it was noted that the effect of the monosodium salt by mouth was only from one-quarter to one-fifth as great as that of thyroxine given intravenously in alkaline solution.

Pure synthetic thyroxine had much less effect by mouth than its monosodium salt.

Squibb's thyroxine for oral use had an effect greater than that of the monosodium salt and less than that of thyroxine given intravenously in alkaline solution. Thus in four patients whose basal metabolism varied from minus 31 per cent to minus 41 per cent (average, minus 35 per cent) during the period of myxedema, it was necessary to administer from 0.46 to 0.73 mg. (average, 0.63 mg.) daily of this product in order to hold the basal metabolism at the normal level. In all four patients the effect of this substance was from two to two and

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34. Schittenhelm, A., and Eisler, B.: Ueber die Resorption des Thyroxins nach oraler Zufuhr, *Ztschr. f. d. ges. exper. Med.* 80:569, 1932.

one-half times as great as that of the monosodium salt by mouth, while in the two patients in whom the comparison was made, it was only about one-half as great as the effect of thyroxine given intravenously in an alkaline solution.

We have previously reported that in the first two patients of this study the effects of desiccated thyroid by mouth and thyroxine intravenously or subcutaneously were the same on the basis of equivalent iodine contents. In the digestion of desiccated thyroid, peptides and polypeptides of thyroxine are formed which have a wide range of solubility.

The solubility of thyroxine compounds appears to be a factor in their absorption from the gastro-intestinal tract and hence in their effect on the basal metabolism.

# BENIGN FAMILIAL POLYCYTHEMIA

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Few instances of familial polycythemia have been reported. No thorough studies have been made of the families of patients with this condition.

Nichamin,<sup>1</sup> in 1907, observed a patient with mild polycythemia whose mother and sister had enlargement of the spleen and cyanosis. No studies were made on the blood of the relatives.

Bernstein,<sup>2</sup> in 1914, recorded what he believed to be the first published report of the familial incidence of polycythemia. The blood of the patient contained 12,500,000 red corpuscles per cubic millimeter and 140 per cent hemoglobin. There were splenomegally and cyanosis. The son of this patient did not have a palpable spleen, but his blood showed 7,500,000 red corpuscles and 120 per cent hemoglobin.

Tancré,<sup>3</sup> in 1917, reported the occurrence of polycythemia in two sisters, one of whom had 13,000,000, and the other 6,100,000, red blood corpuscles per cubic millimeter of blood. He suggested the possibility of familial occurrence.

Engelking,<sup>4</sup> in 1920, examined the members of a family in which the condition was present in three generations: in the grandmother, in the mother and in five children. In the children infantilism also was present, and in some there were disturbances of the functions of the glands of internal secretion.

Doll and Rothschild,<sup>5</sup> in 1922, stated that they had observed a family in which five of six children had Huntington's chorea and two of these had polycythemia.

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From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine of the Harvard Medical School.

1. Nichamin, S. B.: Ein Fall von Erythrämie, *Med. Oboz.*, 1907, no. 6; abstr., *Folia haemat.* **6**:301, 1908.

2. Bernstein, J.: Three Cases of Polycythemia Rubra, *West London M. J.* **19**:207, 1914.

3. Tancré, E.: Zur Polycythemia rubra, *Deutsches Arch. f. klin. Med.* **123**:435, 1917.

4. Engelking, E.: Ueber Polyzythämie als vererbare Störung der inneren Sekretion, *Deutsche med. Wchnschr.* **46**:1140, 1920.

5. Doll, H., and Rothschild, K.: Familiäres Auftreten von Polycythaemia rubra in Verbindung mit Chorea progressiva hereditaria Huntington, *Klin. Wchnschr.* **1**:2580, 1922.

Signorelli,<sup>6</sup> in 1923, observed a man with 9,200,000 red cells per cubic millimeter of blood and 155 per cent (Sahli) hemoglobin. This man's sister had an enlarged spleen and a slight increase in the number of red blood cells but a normal amount of hemoglobin.

Curschmann,<sup>7</sup> in 1923, stated that one of his patients with polycythemia had several relatives whose histories suggested a familial occurrence.

Owen,<sup>8</sup> in 1924, reported the case of a man 46 years old whose blood contained 9,700,000 red corpuscles per cubic centimeter and 120 per cent hemoglobin and whose spleen extended well below the costal margin. The mother and father of this patient had florid complexions. One brother had 6,120,000 red blood cells per cubic millimeter and 110 per cent hemoglobin. His spleen was not palpable. Three sisters had normal blood counts. In no member of this family was the leukocyte count elevated. Owen believed the disease to be familial and directly inherited.

TABLE 1.—*Findings in the Blood in Engelking's Cases*

	Age, Years	Red Blood Cells, per C.Mm.	Hemo- globin, per Cent	White Blood Cells, per C.Mm.	Hema- to- crit, per Cent
1. Mother.....	49	8,160,000	98	8,600	57
2. Son.....	21	11,390,000	150	9,200	84
3. Son.....	17	9,870,000	140	7,500	80
4. Daughter.....	10	12,160,000	150	9,500	76
5. Son.....	8	4,400,000	65	7,400	45
6. Son.....	5	8,010,000	140	11,400	70

Wieland,<sup>9</sup> in 1924, made a further report on the family studied by Engelking. He stated that it was probable that polycythemia existed in three generations, and he believed the disease to be a constitutional hereditary defect. Table 1 illustrates the findings in these cases.

Herz,<sup>10</sup> in 1925, studied three families in which he believed there was a tendency toward the occurrence of the disease. However in no case was the spleen enlarged, and in only one did the hemoglobin value exceed 90 per cent. In only two of the twelve members of the three families did the number of red blood cells exceed 6,800,000 per cubic

6. Signorelli, E.: Su dei casi familiari d'iperglobulia con splenomegalia e cianosi, *Haematologica* 4:437, 1923.

7. Curschmann, H.: Ueber konstitutionelle und familiäre Hyperglobulie, *Med. Klin.* 19:133, 1923.

8. Owen, T.: A Case of Polycythemia Vera with Special Reference to the Familial Features and Treatment with Phenylhydrazine, *Bull. Johns Hopkins Hosp.* 35:258, 1924.

9. Wieland: Ueber Polycythaemia idiopathica beim Kinde, *Ztschr. f. Kinderh.* 38:647, 1924.

10. Herz, O.: Polycythaemia idiopathica, *Ztschr. f. Kinderh.* 40:151, 1925.

millimeter. In every case the percentage of polymorphonuclear neutrophils was normal.

Kretschmer,<sup>11</sup> in 1925, recorded polycythemia in three children in one family. The father was not examined, and the mother was normal. In only one of the three children was the spleen palpable. In each case there was a low white blood cell count, ranging from 4,700 to 5,400. The differential counts showed normal values for polymorphonuclear neutrophils. In two of the children the number of polymorphonuclear eosinophils was elevated to 9.6 and 5 per cent respectively. Two of the children had hemoglobin values of 140 per cent and red blood cell counts varying from 9,400,000 to 10,200,000.

Weil and Stieffel,<sup>12</sup> in 1926, reported polycythemia in a brother and sister. The man had a red blood cell count fluctuating between 5,500,000 and 7,000,000, whereas his sister had a count of 6,440,000. Only in the man was the spleen palpable.

Weber<sup>13</sup> discussed the constitutional and familial factors in primary and secondary polycythemia and recognized that a familial incidence is rare. He gave a bibliography and mentioned two instances of a familial tendency which we have not cited. There are records in the literature of at least eleven families in which polycythemia vera was thought to be familial. (There are other reports, but insufficient evidence was presented to indicate that the condition should be considered familial.) The report by Nichamin<sup>1</sup> was not verified by studies of the blood and it is therefore difficult to be sure that the condition was polycythemia vera. Although Signorelli's<sup>6</sup> case was undoubtedly one of polycythemia vera, there seems to be little justification for assuming that the patient's sister, who had a red blood cell count of 5,800,000 and 94 per cent hemoglobin, also had the disease. Curschmann<sup>7</sup> did not record results of examination of the blood to support his hypothesis of familial incidence. The brother of Owen's<sup>8</sup> patient cannot be considered, on the evidence presented, to have had polycythemia vera. His red blood cell count, although high, was within normal limits, and the spleen was not enlarged. Herz<sup>10</sup> did not present conclusive evidence that he was dealing with polycythemia vera or that the condition was familial.

If one judges the reported cases from a critical point of view, it appears that in only six instances (those reported by Bernstein, Tancré, Engelking and Wieland, Doll and Rothschild, Kretschmer, and Weil

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11. Kretschmer, M.: Ueber familiäre, idiopathische Polycythämie im Kindesalter, *Ztschr. f. Kinderh.* **40**:225, 1925.

12. Weil, E., and Stieffel, R.: Deux cas de pléthore polyglobulique familiale, *Bull. et mém. Soc. méd. d. hôp. de Paris* **50**:1248, 1926.

13. Weber, F. P.: The Constitutional and Familial Factor in Primary and Secondary Polycythemia Rubra, *M. Press* **124**:128, 1927.



and Stieffel) has polycythemia with splenomegaly been conclusively shown to be a familial trait.

We had the opportunity of studying a family of ten members in which polycythemia was shown to exist in seven. The studies included, for each member of the family, at least seven determinations, over a period of one year, of red blood cell, white blood cell and hemoglobin values, together with differential leukocyte counts, enumeration of reticulocytes and measurement of the hematocrit percentage. The blood cell counts were made with pipets and counting chambers certified by the United States Bureau of Standards. Detailed histories were taken, and physical examinations, examinations of the urine, complement-fixation tests on the blood serum, quantitative measurements of the bilirubin and icterus index and study of the gastric secretions were made.

#### REPORT OF A CASE

The first member of the family studied (case 3, tables 2, 3 and 4) was a 24 year old white unmarried Italian student who presented strikingly few complaints. Accidentally he was found to have an elevated red blood cell count, averaging 7,800,000. He had moderately severe headache two or three times a week.

*History.*—The patient was born in Italy; at the age of 5 years he emigrated to the state of New York, where he had lived with the other members of his family for nineteen years before we saw him. Except for headaches and a few minor illnesses he had been perfectly well. As a child he had measles, mumps, influenza and tonsillitis. Twelve years before we saw him his tonsils and adenoids were removed. During the past year a deviated nasal septum had been operated on. No undue bleeding or other complications followed these operations.

He had never had diphtheria, scarlet fever, smallpox, rheumatic fever, malaria, chorea, typhoid fever, pneumonia, pleurisy, tuberculosis or any other severe illness. A review of his past history as regards the various organs and systems of the body revealed no significant information. There had been no loss or gain in weight during the past two years.

The patient had had recurrent headaches since early childhood. They were characterized by dull pain, usually over the temporal region, on either the right or the left side, but more frequently on the left. The headaches did not occur at regular intervals. They persisted for a few hours and were relieved by sleep and sometimes by eating or by cold applications to the head. Their occurrence was not related to eye-strain, to constipation or to infections of the upper respiratory tract. They were not brought on by overactivity or by any other factors within his knowledge. He stated that his color had always been ruddy. He perspired freely, particularly over the forehead and the palms. He had noticed occasional tinnitus during the past few years.

*Family History.*—The patient was the oldest child in a family of ten. His father, aged 51, his mother, aged 50, and seven younger brothers and sisters were all living and well. There was no family history of tuberculosis, diabetes, cancer, hemorrhagic disorders, heart disease, disease of the kidneys, arthritis or anemia. The father and the paternal grandfather had florid complexions. The mother, a younger brother and a maternal aunt had headaches similar to those of the patient.

*Physical Examination.*—The patient was well developed, well nourished and alert and was carrying on his activities as a student without apparent discomfort. The conjunctivae and other mucous membranes were somewhat more highly colored than is normal. There were slight enlargement and moderate injection of adenoid tissue in the region of the left tonsil. The heart and lungs were normal. The blood pressure was 114 systolic and 74 diastolic. The abdomen was normal except for a palpable spleen, which was firm and not tender. On quiet respiration

TABLE 2.—*Red Blood Cells, White Blood Cells and Hemoglobin Determinations on Members of the Patient's Family\**

Cases	Age, Years									Average
1. Father.....	52	7,230,000	7,200,000	6,890,000	6,860,000	6,590,000	6,910,000	6,730,000	6,910,000	
		7,650	8,200	6,725	11,950	7,850	8,150	6,650	8,167	
			15.76	14.88	15.29	15.76	14.20	13.60	14.91	
2. Mother.....	51	6,350,000	5,520,000	6,450,000	5,480,000	6,220,000	5,440,000	5,690,000	5,920,000	
		6,400	7,750	7,500	7,000	6,475	6,550	.....	6,954	
			14.82	14.66	14.35	14.51	14.51	14.74	14.59	
3. Son (patient)	24	8,000,000	7,980,000	8,390,000	7,670,000	7,050,000	8,050,000	7,500,000	7,803,000	
		7,600	5,900	6,940	6,750	11,150	10,050	11,500	8,555	
			15.76	16.07	15.76	15.99	15.76	14.35	15.61	
4. Daughter....	22	7,450,000	7,210,000	7,230,000	7,410,000	6,270,000	7,080,000	7,110,000	7,100,000	
		8,600	6,750	8,050	6,150	6,400	5,450	7,700	7,014	
			12.32	12.79	12.48	12.64	13.26	12.79	12.71	
5. Son.....	18	7,750,000	7,650,000	7,260,000	6,950,000	6,920,000	6,770,000	7,700,000	7,280,000	
		6,750	7,600	9,400	7,750	13,050	9,500	8,050	8,871	
				14.04	13.42	14.35	14.51	14.35	14.13	
6. Daughter....	16	5,140,000	4,490,000	4,880,000	5,210,000	4,820,000	5,160,000	4,960,000	4,950,000	
		8,600	6,000	6,500	7,450	8,000	7,100	.....	7,275	
			12.17	12.10	12.48	12.79	11.70	12.79	12.34	
7. Daughter....	13	6,560,000	5,620,000	5,990,000	6,180,000	5,900,000	5,890,000	5,760,000	5,980,000	
		6,800	9,850	11,625	17,050	15,500	10,500	8,700	11,439	
			13.26	13.57	13.26	14.35	13.88	15.29	13.93	
8. Son.....	10	6,700,000	6,700,000	6,750,000	6,620,000	6,320,000	7,230,000	7,220,000	6,750,000	
		6,400	8,000	8,550	10,850	9,150	6,700	7,100	8,071	
				11.70	12.87	13.26	12.17	12.48	12.50	
9. Daughter....	9	5,510,000	4,850,000	5,540,000	4,780,000	5,350,000	5,570,000	5,064,000	5,240,000	
		6,800	9,050	8,450	11,300	7,950	8,550	6,000	8,300	
			13.10	13.18	12.48	13.26	12.79	12.79	12.93	
10. Daughter....	11	5,270,000	5,630,000	4,960,000	5,000,000	5,320,000	5,440,000	4,730,000	5,190,000	
		10,400	7,700	6,800	9,750	6,100	7,600	9,850	8,314	
			13.26	13.10	13.25	12.95	13.42	14.04	12.64	13.24

\* Results of six observations on each person, the first in 1931, and the last five in the period from April to July, 1932. For each patient, the upper line of figures indicates red blood cells; the middle line, white blood cells, and the lower line, the hemoglobin (Gm. per 100 cc.).

it extended 4 cm. below the costal margin in the midclavicular line. The edge of the liver could not be felt, but by percussion it was recognized to be at the costal margin.

Ophthalmoscopic examination revealed no abnormalities except that the retinal veins were possibly a little fuller and darker than is normal.

*Laboratory Examination.*—The results of study of the blood, of the gastric secretions and of the basal metabolic rate are recorded in tables 2 and 3.

The urine was cloudy and amber colored and had a specific gravity of 1.020. It gave negative results when tested for albumin, sugar, diacetic acid, acetone and bile. The sediment showed occasional white blood cells and no casts or red blood cells.

TABLE 3.—*Differential Leukocyte and Reticulocyte Counts, Gastric Analysis, Basal Metabolic Rate and Physical Signs in Members of the Patient's Family*

in Members of the *F. attenuatus* Family

Cases	Age, Years	Reticulo-cytes, per Cent	Platelets	Differential Leukocyte Count						Blood Pressure	Significant Physical Signs	Gastric Analysis 20 to 40 Minutes After Alcohol Meal	
				Polymorphonuclears			Mono-cytes, per Cent	Lympho-cytes, per Cent	Basal Metabolic Rate				
				Neutro-phils, per Cent	Baso-phils, per Cent	Eosino-phils, per Cent							
1. Father.....	52	2.4	Normal	62.5	...	2.0	7.5	28	+ 1 + 3.5	129/85	Very red face and hands; retinal vessels full and dark	10	68
2. Mother.....	51	1.6	Normal	66.5	0.5	1.0	4.0	28	+ 7.3 +12.4	112/76	Moderately red face	No analysis made	
3. Son(patient) 24	...	...	Moderately increased	63	...	4	12	21	— 0.9 — 4.0 — 6.0	114/74	Spleen 4 cm. below costal margin	44	51
4. Daughter... 22	2.2	2.2	Moderately increased	63.5	1.5	1.5	2.5	31	+ 2.3 + 0.6	114/70	Spleen 3 cm. below costal margin; liver 1 cm. below costal margin	18	80
5. Son..... 18	1.0	1.0	Normal	57	2.0	4.0	16	21	+13.1 +15.0	122/76	Spleen 1.5 cm. below costal margin	93	104
6. Daughter... 16	0.6	0.6	Normal	58	1.5	3.0	6.5	31	+ 9.7 +12.8	126/90	None	No analysis made	
7. Daughter... 13	1.2	1.2	Moderately increased	56	3.0	2.5	8	30.5	+ 3.3 + 2.2	124/65	Spleen 1.5 cm. below costal margin; retinal vessels full and dark	30	39
8. Son..... 10	2.4	2.4	Moderately increased	64	1.0	3.0	10	22.0	—11.5 — 8.3	110/74	Retinal veins dark	33	50
9. Daughter... 9	0.2	0.2	Normal	50	1.5	4.0	3.5	41.0	+10.7 + 4.9	96/64	Spleen 1 cm. below costal margin; retinal veins dark	No analysis made	
10. Daughter... 11	1.4	1.4	Slightly diminished	64	2.0	1.0	8	25.0	— 7.4 — 4.8	94/59	None	44	55

The icterus index of the blood serum was 10. The bilirubin content was less than 1 mg. per hundred cubic centimeter of serum. Hemolysis began in a 0.46 per cent solution of sodium chloride and was complete in a 0.22 per cent solution.

The Wassermann reaction of the blood was negative.

The bleeding time was two and a half minutes.

*Summary.*—The patient presented a history of frequently recurring headaches, occasional tinnitus and excessive perspiration of the palms and the face. The physical findings of importance were redness of the mucous membranes, slightly dilated and darkened retinal vessels and an enlarged spleen. The laboratory findings showed a distinctly elevated red blood cell count and a hematocrit value greater than normal.

#### SIGNIFICANT FINDINGS IN OTHER MEMBERS OF FAMILY

*Paternal Grandfather.*—The paternal grandfather, aged 103, was living and well. He had always had a very red face. He was not available for examination.

*Paternal Grandmother.*—The paternal grandmother died of hemiplegia at the age of 96.

*Maternal Grandfather.*—The maternal grandfather died of "liver trouble" at the age of 50.

*Maternal Grandmother.*—The maternal grandmother died of "heart trouble" at the age of 67.

*Father (case 1).*—The father's history and the results of examination were not remarkable except for the presence of extreme redness of the face and hands for many years, slightly enlarged and dark retinal vessels, a persistently high red blood cell count, averaging 6,910,000, and a hematocrit value of 50.3 per cent. The spleen and liver were not palpable. The heart and lungs were normal.

*Mother (case 2).*—The mother, aged 51, as a girl had been given the nickname "Reddie" because of the intense redness of the face, which had persisted. For twenty-five years she had frequently had bilateral headaches. A sister and her two sons had similar headaches. The results of examination were not remarkable except for a red blood cell count averaging about 5,920,000. The hematocrit value was perhaps slightly elevated, the value being 46.7 per cent. The heart and lungs were normal. The spleen and liver were not palpable.

*Sister, Aged 22 (case 4).*—There were no significant data in the history. Examination revealed an enlarged spleen extending on quiet respiration to 3 cm. below the costal margin in the midclavicular line. It was firm and not tender. The liver extended 1 cm. below the costal margin. The red blood cells averaged 7,100,000, and the hematocrit value was 49.5 per cent. The heart and lungs were essentially normal.

*Brother, Aged 18 (case 5).*—There was a history of occasional attacks of giddiness. The youth had a "pounding" sensation in the head as a result of exertion. He had recurrent unilateral headaches. Examination showed the mucous membranes and the exposed areas of skin to be more deeply colored than is normal. The retinal vessels were somewhat dilated and dark. The spleen was felt 1.5 cm. below the costal margin in the anterior axillary line; it was firm and not tender. The liver was at the costal margin. The heart and lungs were essentially normal. There was an increased amount of free hydrochloric acid in the gastric contents. The red blood cell count and the hematocrit value were distinctly elevated, being 7,280,000 and 57 per cent respectively.

*Sister, Aged 16* (case 6).—The history was not significant. Examination gave essentially normal results. The blood cell count was not elevated. The spleen was not palpable.

*Sister, Aged 13* (case 7).—The history was not remarkable. Examination showed moderate injection of the conjunctivae together with dilatation and darkness of the retinal veins. The spleen, which was firm and not tender, extended 1.5 cm. below the costal margin in the anterior axillary line. The liver was at the costal margin and slightly tender. The red blood cell count averaged 5,980,000, and the hematocrit reading was 46.9 per cent. The leukocyte count fluctuated from 6,800 to 17,050, the average being 11,440.

*Brother, Aged 10* (case 8).—The history was not significant. The results of physical examination were essentially normal. The hematocrit value was normal, but the red blood cell count was elevated, averaging 6,790,000.

*Sister, Aged 9* (case 9).—The history was not significant. The retinal veins were dark. The heart and lungs were normal. The spleen was definitely firm and not tender; it was felt 1 cm. below the costal margin. The liver was not palpable. The hematocrit value was normal. The red blood cell count was within normal limits.

*Sister, Aged 11* (case 10).—The history and the results of physical examination were essentially normal. The spleen and liver were not enlarged. The red blood cell count was normal.

#### ADDITIONAL DATA CONCERNING THE CASES REPORTED

The history does not show that any member of the family had typhoid, malaria or any other disease commonly associated with enlargement of the spleen. For none was there a history suggesting familial jaundice. The reticulocytes did not exceed 2.4 per cent in any case. The icterus index did not exceed 10 in any case, and in only one (case 3) did the value exceed 5. The bilirubin was uniformly below 1 mg. per hundred cubic centimeters of blood serum. The Wassermann test of the blood serum was negative in each instance. In nine of the cases the blood belonged to iso-agglutination group IV (Moss classification), and in case 6 the blood was not grouped. In only one case (case 7) was the number of white blood cells abnormal. In no case was the differential leukocyte count markedly abnormal. The relative numbers of polymorphonuclear neutrophils and eosinophils were not increased above normal values. All of the members of the family were vegetarians, caring little for and only occasionally eating meat. Aside from this, their dietary history was not remarkable.

#### COMMENT

With reference to the existence of polycythemia and enlargement of the spleen, the members of this family may be classed in four groups, as presenting:

- (A) Polycythemia with enlargement of the spleen: four cases (3, 4, 5 and 6).
- (B) Polycythemia without enlargement of the spleen: three cases (1, 2 and 8).
- (C) No polycythemia but enlargement of the spleen: one (case 9).
- (D) No polycythemia on enlargement of the spleen: two cases (6 and 10).

Although the spleen was not felt in the father and mother (cases 1 and 2), this does not necessarily indicate that it was not or had not been enlarged. Both of these persons were short and somewhat obese, which made abdominal palpation more difficult than in the younger members of the family. Neither can we be certain that in the persons in groups C and D there were no potential possibilities of the development of polycythemia. Case 9, in which there was no polycythemia but in which the spleen was palpable, suggests this.

The fact that all of the members of the family were almost exclusively vegetarians may be of significance. If antianemic sub-

TABLE 4.—*Hematocrit Reading, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin and Mean Corpuscular Hemoglobin Concentration in Members of the Patient's Family*

Case	Age, Years	Red Blood Cells, per C.Mm.	Hemo-globin, Gm. per 100 Cc.	Hema-tocrit, per Cent	Mean Corpus-cular Volume, Cubic Microns	Mean Corpus-cular Hemo-globin, Micro-grams	Mean Cor-puscular Hemo-globin Concen-tration, per Cent
1. Father.....	52	6,780,000	13.57	50.30	74.2	20.0	27.0
2. Mother.....	51	5,450,000	14.59	46.66	85.6	26.8	31.3
3. Son (patient)	24	7,980,000	15.75	50.08	62.8	19.7	31.4
4. Daughter....	22	7,110,000	12.71	49.55	69.7	17.9	25.7
5. Son.....	18	8,070,000	14.51	57.00	70.6	18.0	25.5
6. Daughter....	16	.....	.....	.....	....	....	....
7. Daughter....	13	5,620,000	15.37	46.93	83.5	27.3	32.8
8. Son.....	10	6,430,000	12.48	42.57	66.2	19.4	29.3
9. Daughter....	9	5,200,000	12.79	39.60	76.2	24.6	32.3
10. Daughter....	11	4,880,000	12.48	45.18	92.6	25.6	27.6
Normal* (10 men).....		5,000,000	14.82	46.0	92.0	29.8	32.4
Normal (10 women).....		4,600,000	13.10	42.8	93.0	28.5	31.0

\* As determined in this laboratory. See Heath, C. W.: *New England J. Med.* **209**: 173 (July 27) 1933.

stances such as liver or iron had been administered, the condition might have been exaggerated, as the color index and the mean corpuscular hemoglobin concentration in all of the cases were distinctly low. The mean corpuscular volume was also below the lower limits of normal in five cases, and the mean corpuscular hemoglobin was decreased in seven of the nine cases in which these measurements were made (table 4).

It is of interest that all of the male members of the family (cases 1, 3, 5 and 8) and half of the female members (cases 2, 4 and 7) had polycythemia.

We were not able to study any of the more distant relatives because of their residence in Europe. Therefore, we are unable to say with certainty that other members were affected. The history, however, suggests that the paternal grandfather may have had the condition.

The cases recorded by Doll and Rothschild<sup>5</sup> and those studied by Engelking<sup>4</sup> and Wieland,<sup>9</sup> in which the polycythemia was associated with another inherited or familial trait (in one group, hereditary chorea, and in the other, infantilism) suggest that a defect in the germ plasma may play a part in the pathogenesis of the condition. No such associated defects were observed in our cases, with the possible exception of headache, which was present in the mother and two of her sons (cases 2, 3 and 5) and in the mother's sister.

Although there seems to be no doubt that polycythemia, together with enlargement of the spleen, was a familial trait in these cases, certain characteristic features ordinarily associated with polycythemia vera were absent. The benign course of the condition, which had undoubtedly existed for many years, the absence of leukocytosis, the normal numbers of polymorphonuclear neutrophils and eosinophils, the uniformly normal hemoglobin values and the normal basal metabolic rates speak against the diagnosis of typical polycythemia vera. It seems necessary to assume either that the members of this family had an unusual form of polycythemia vera, or, as seems more probable to us, that they presented a benign condition for which we suggest the name "benign familial polycythemia."

#### SUMMARY

1. A critical review of the reported examples of familial polycythemia has been presented.
2. Observations on the blood, together with other clinical studies, of ten members (two generations) of a family in which polycythemia and splenomegaly were present are reported. The existence of polycythemia in an earlier generation of the family is suggested by the history.
3. This family differed from those previously described in that characteristics of polycythemia vera, other than the increased number of red blood corpuscles and enlargement of the spleen, were not present.
4. The term "benign familial polycythemia" is suggested to distinguish this condition from polycythemia vera and from polycythemia due to recognized causes.

# TEMPERATURE OF THE GASTRO- INTESTINAL TRACT

THE EFFECT THEREON OF HOT AND COLD FOODS AND OF  
PHYSICAL THERAPEUTIC AGENTS

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A wide difference of opinion exists among surgeons and internists concerning the value and action of the ice bag and the different forms of heat, applied locally, in the treatment of acute appendicitis, ulcer of the stomach or duodenum and other pathologic processes within the abdomen. In many patients, gastro-enteric upsets occur after the ingestion of ice cream, ices and iced drinks. This research, therefore, was undertaken in order to ascertain the influence exerted on gastro-intestinal temperatures by (a) the ingestion of hot and cold foods and drinks, and by (b) the local application of cold and of various forms of heat.

Eichler and Schemel<sup>1</sup> measured gastric temperature by means of the "fever registration apparatus" of Siemens and Halske. Their results showed that the normal gastric temperature lies between 98.6 and 99.2 F. This temperature was increased slightly by the application of the steam jet or by local irradiation with an arc light, and was decreased slightly by epigastric application of the apparatus of Winternitz, an ice bag or a trunk pack. The maximum period of application was 30 minutes; the greatest change in gastric temperature, 1.6 F.

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1. Eichler and Schemel: Ueber die Beeinflussung der Magentemperatur durch verschiedene hydrotherapeutische Applikationen und ihre Messung mit dem "Fieberregistrierapparat" nach Siemens u. Halske, Deutsche med. Wchnschr. **37**: 2371, 1911.



Bergeim<sup>2</sup> introduced a thermocouple of copper and iron-constantan into the stomach in the tip of a Rehfuß tube, and then measured gastric temperatures. He reported that "after the ingestion of cold foods or liquids of any kind, a half hour or more may be required to reach body temperature."

Stengel and Hopkins<sup>3</sup> used a similar thermocouple placed in the tip of an Einhorn tube, and determined its position in the stomach by means of a fluoroscope. Their results on 5 subjects showed the temperature of both the fundus and the pylorus to lie between 98.4 and 100.4 F. They also studied the influence on gastric temperature of ingested ice water and of hot and cold foods when included in a meal. Application of ice bags to the epigastrium for 45 minutes decreased the gastric temperature by from 1.6 to 1.8 F. Hot water bags, under the same conditions, had a practically negligible effect.

Sheard<sup>4</sup> described a copper-constantan thermocouple, and mentioned its use for measurement of gastric temperature.

#### TECHNIC

In these studies, use was made of a resistance thermometer of insulated nickel wire mounted in a silver tube 1 inch (2.5 cm.) in length and  $\frac{1}{4}$  inch (0.63 cm.) in outside diameter. This thermometer was attached to a resistance thermometer recorder by means of insulated copper wires contained in a flexible rubber tube approximately  $\frac{1}{4}$  inch in external diameter. The recorder had a temperature range from -10 to 120 F., and would record any temperature to which the gastro-intestinal tract might be subjected. The greatest possible error of the instrument was  $\pm 0.6$  F. over its entire range, and  $\pm 0.2$  F. within the range of from 90 to 110 F.; it was sensitive to a change of 0.1 F. The ruled paper passed through the recorder at the rate of 6 inches (15.24 cm.) per hour. It was graduated in increments of 1 F., and the position of the graph was interpolated to 0.1 F. The recorder was a stock article, and the thermometer was especially constructed for this research; both were manufactured by the Leeds and Northrup Company.

The thermometer and that portion of the rubber tube which was swallowed were sterilized by immersion at room temperature in a solution of hexylresorcinol S. T. 37. They were washed with sterile water just before being swallowed, since subjects complained of the prolonged action of the glycerol in the hexylresorcinol solution on the lips and pharynx when the tube was kept in the alimentary tract for an hour or longer.

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2. Bergeim, O.: Gastric Response to Foods: I. The Determination and Significance of Intra-gastric Conductance, *Am. J. Physiol.* **45**:1, 1917.

3. Stengel, A., and Hopkins, A. H.: A New Method for Determining the Intra-gastric Temperature in Man, with Some Observations on Its Variations After Ingestion of Hot and Cold Liquids and During Digestion, *Am. J. M. Sc.* **153**:101,

4. Sheard, C.: An Instrument and a Method for Measuring Intramural, Intravenous, Superficial and Cavity Temperatures, *Am. J. Clin. Path.* **1**:209, 1931. 1917.

For measurement of the gastric temperature, the thermometer was introduced in the same manner as a stomach tube. For measurement of the temperature of the upper part of the intestine, the thermometer was introduced in the same manner as a duodenal tube for nonsurgical biliary drainage. In order to protect the tube from abrasion, the portion between the teeth was surrounded by a loosely fitting piece of soft rubber tubing. For measurement of the temperature of the sigmoid, the thermometer was introduced through a sigmoidoscope well past the sphincter of O'Beirne, the subject being in either the Sims or the knee-chest position. The wall of the sigmoid was then permitted to collapse about the thermometer. Oral temperature was measured with a clinical thermometer.

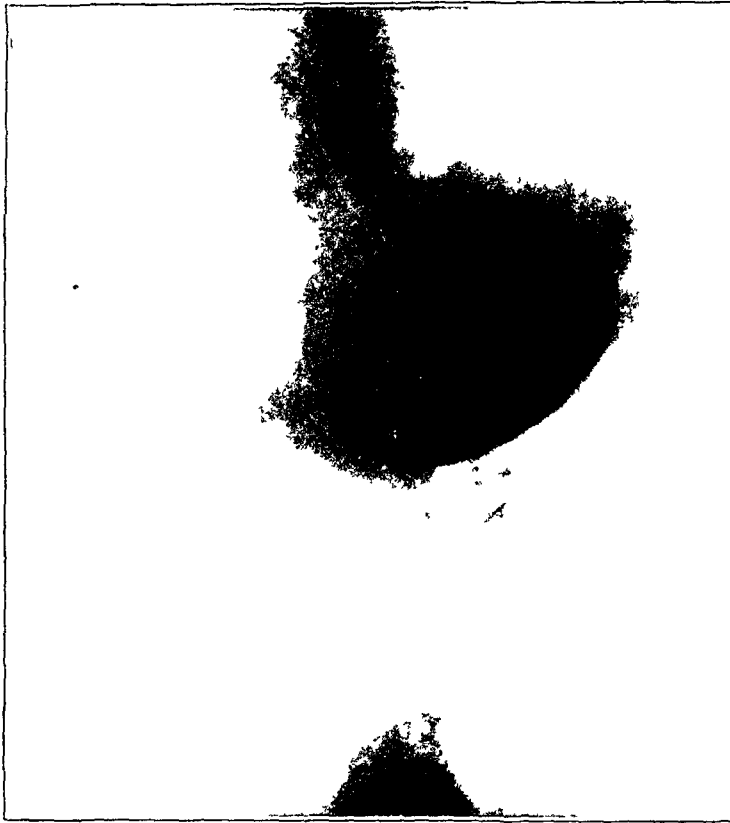


Fig. 1.—Roentgenogram showing meal of barium sulphate in the stomach and a thermometer in the jejunum.

The subjects were chiefly technicians and students in the schools of medicine and nursing. They were all healthy and active. In all the experiments except those on the sigmoid, the subject had an empty stomach.

In the experiments with ice water, ice cream and coffee, the subjects were in a sitting position; they were requested to ingest these substances as rapidly as possible without discomfort, and the time required for ingestion was measured with a stopwatch. In all the other experiments on the stomach and the upper part of the intestine, the subjects were in a supine position.

In experiments concerning the influence of physical therapeutic agents on the gastric temperature, the actual position of the stomach was determined by roentgenography. One or more days prior to the actual experiment, a one cent coin was fastened over the umbilicus; a test meal of barium sulphate was given on an

empty stomach. Fluoroscopy was performed; roentgenographs of the stomach were taken in the usual manner, with the patient prone and supine. The position of the stomach with respect to both the umbilicus and the bony landmarks was thereby ascertained. During the actual experiment, the agent was applied directly over the true epigastric region.

In measurement of the temperature of the upper part of the intestine, and in study of the influence of physical therapeutic agents on that temperature, the following technic was found most satisfactory for determining the position of the thermometer in the intestine: One or more days prior to the actual experiment, roentgenographs of the stomach were taken as described, with the patient both prone and supine. On the day of the actual experiment, after the thermometer had been passed to the 75 cm. mark, roentgenographs were taken, with the patient both prone and supine, usually with a one cent coin fastened over the umbilicus, and the films were developed immediately. By comparison of the pictures taken with the patient in the prone position, it was possible to determine whether the thermometer had passed into the intestine, and if it had, the region it had reached (duodenum or jejunum). If the thermometer had not left the stomach, the tube was drawn up to the 55 cm. mark and then reswallowed, in the usual manner, to the 75 cm. mark; another set of roentgenographs was then taken. The pictures with the patient in the supine position were used to determine the exact region of the body surface on which to apply the physical therapeutic agent so that the thermometer lay in the center of the area of action.

All temperatures are reported on the Fahrenheit scale.

#### TEMPERATURE OF THE GASTRO-INTESTINAL TRACT

Gastric temperature was taken as recorded on the graph as soon as the recorder had come to equilibrium after the thermometer had been swallowed. In 129 men, the maximum gastric temperature was 101.8 F., the minimum 97.8 and the average 99.2. In 128 women, the maximum was 102.2 F., the minimum 97.5, and the average 99.4. In table 1, the subjects have been classified according to their gastric temperature in groups, each with a range of 1 F. With each sex, the gastric temperature was between 99 and 99.9 F. in approximately six tenths of the subjects, and between 98 and 100.9 F. in over nine tenths of the subjects.

*Comparison of Gastric with Oral Temperature.*—In 124 of the men and all of the women, the temperatures of both the stomach and the mouth were taken. In both sexes, the gastric temperature usually was higher than the oral temperature, the average difference being 0.9 F. in the men and 1.25 F. in the women. In individual men, the gastric temperature was as much as 0.8 F. lower and as much as 3.1 F. higher than the oral temperature. In individual women, the gastric temperature was as much as 0.6 F. lower and as much as 4.4 F. higher than the oral temperature. In table 2, the subjects have been divided according to the magnitude of the deviation of the gastric temperature from the oral temperature, each group having a range of 1 F. The percentage of the subjects falling into each group is shown.

*Variation in Gastric Temperature.*—The gastric temperature of a subject may vary during a comparatively short period of time. In the forty experiments summarized here, the variation was taken as the difference between the highest and the lowest temperatures recorded on the graph while the thermometer was in the subject's stomach. In 15 men, the experiments extended over periods of time ranging from 0.5 to 3.5 hours; variations as great as 3.8 F. were noted. In 25 women, each experiment occupied from 0.75 to 2 hours. Variations as great as 1.3 F. were observed. With both sexes, some subjects showed no variation, the graph demonstrating that no change in temperature occurred.

*Temperature of the Upper Part of the Intestine.*—The intestinal temperature was taken as recorded on the graph after the roent-

TABLE 1.—*Gastric Temperature*

Temperature, F.	Men	Women
97-97.9.....	3	1
98-98.9.....	28	21
99-99.9.....	76	77
100-100.9.....	20	21
101-101.9.....	2	7
102-102.9.....	0	1

TABLE 2.—*Deviation of Gastric Temperature from Oral Temperature*

Deviation, F.	Men, per Cent	Women, per Cent
-0.1 to -0.9.....	8.06	3.13
0.....	4.84	2.34
0.1 to 0.9.....	40.32	35.16
1.0 to 1.9.....	36.29	41.41
2.0 to 2.9.....	9.68	14.06
3.0 to 3.9.....	0.81	3.13
4.0 to 4.9.....	0	0.78

genograph had demonstrated the thermometer to be in the upper part of the intestine. Measurements were made on 34 men (33 duodenal and 1 jejunal measurement) and 19 women (16 duodenal and 3 jejunal measurements).

In the men, the intestinal temperature ranged between 98 and 100.1 F., with an average of 99.1 F. The intestinal temperature was exactly the same as the gastric in 12 cases, higher than the gastric temperature in 11 cases and lower than the gastric temperature in 11 cases. The maximum difference between the temperature of the two organs was 0.4 F.; the average difference, less than 0.1 F.

In the women, the intestinal temperature ranged between 98 and 99.9 F., with an average of 98.9 F. The intestinal temperature was exactly the same as the gastric temperature in 5 cases, higher than the gastric temperature in 6 cases and lower than the gastric temperature in 8 cases. The maximum difference between the temperatures of the two organs was 0.9 F.; the average difference, less than 0.1 F.

*Sigmoidal Temperature.*—The sigmoidal temperature was taken as that recorded on the graph as soon as the recorder had come to equilibrium after the thermometer had passed through the sphincter of O'Beirne. In 6 normal subjects (3 men and 3 women), the average temperature of the sigmoid was 101.2 F., the maximum 101.5 and the minimum 100.8. The sigmoidal temperature was always higher than the oral temperature, on the average by 2.9 F.; the least difference between the two temperatures was 2 F.; the greatest difference, 3.5 F.

#### INFLUENCE OF HOT AND COLD FOODS ON GASTRIC TEMPERATURE

*Ice Water.*—The subjects included 27 men and 25 women. Each subject drank 250 cc. of ice water, the temperature of which was measured by means of a mercury thermometer immediately prior to ingestion. An immediate, marked decrease in gastric temperature resulted; this was followed by a rise, at first quite rapid, then progressively slower; finally the curved graph again became a straight line which recorded exactly the same temperature for at least 10 minutes. This constant temperature was taken as the final temperature or temperature after recovery; it was approximately the same as the initial temperature, but tended to be a few tenths of a degree lower than the latter. Thus, with each sex, the average of the final temperatures was 0.2 F. lower than the average of the initial temperatures. The time measured on the graph from the drop in temperature on ingestion of the ice water to the beginning of the constant final temperature was the recovery time. The results of these experiments are summarized in table 3.

The decrease in gastric temperature and the recovery time apparently did not depend on either the temperature of the ice water or the time required for its ingestion. Each of two women ingested the coldest ice water used in the experiments with their sex (temperature, 32.9 F.) in exactly the same time (0.34 minute); they yielded, respectively, the maximum and the minimum decrease in gastric temperature (42.5 and 7.2 F.); the subject with the maximum decrease had a recovery time of 31.3 minutes, while the subject with the minimum decrease had a recovery time of 65.1 minutes, the longest recovery time in the entire group of fifty-two experiments.

*Ice Cream.*—The subjects were 26 men and 25 women. Each subject ate 90 Gm. of ice cream, that quantity being the standard hospital portion. The temperature of the ice cream was measured by means of a mercury thermometer immediately prior to ingestion. The graph obtained was somewhat similar to that yielded by the ingestion of ice water, except that the initial decrease in temperature was less marked. As with ice water, the final temperature of the stomach was approxi-

mately the same as its initial temperature, but tended to be a few tenths of a degree lower than the latter; with each sex, the average difference between initial and final temperature was 0.2 F.

With 12 men and 4 women, the decrease in gastric temperature on the ingestion of ice cream did not exceed the maximum variation in gastric temperature previously reported for their respective sexes. However, their graphs showed the typical response to a cold stimulus, i. e., an immediate decrease in gastric temperature on eating the ice cream followed by a slow return to approximately the initial gastric temperature. Therefore, these experiments have been included in the series which is also summarized in table 3.

TABLE 3.—*Effect of Ice Water and Ice Cream on the Gastric Temperature*

Substance Ingested	Observation	Sex	Maximum	Minimum	Average
Ice water	Temperature of ingested ice water, F.	{ Male.....	40.1	32.5	34.0
		{ Female.....	34.7	32.9	33.4
	Ingestion time, minutes	{ Male.....	1.12	0.11	0.33
		{ Female.....	1.35	0.21	0.59
	Decrease in gastric temperature, F.	{ Male.....	37.9	9.8	27.6
		{ Female.....	42.5	7.2	22.9
	Recovery time, minutes	{ Male.....	62.0	10.2	38.1
		{ Female.....	65.1	25.6	39.8
Ice cream	Temperature of ingested ice cream, F.	{ Male.....	23.0	—0.4	9.5
		{ Female.....	27.5	—0.4	7.7
	Ingestion time, minutes	{ Male.....	6.02	1.50	3.24
		{ Female.....	8.50	1.96	4.30
	Decrease in gastric temperature, F.	{ Male.....	43.8	1.0	8.3
		{ Female.....	14.9	0.2	5.1
	Recovery time, minutes	{ Male.....	52.8	11.5	32.6
		{ Female.....	57.0	20.0	36.1

The magnitude of the decrease in gastric temperature apparently depends on the temperature of the ice cream, the time taken for its ingestion and the subject, as may be seen from the following experiments, which are included in the series.

The apparent influence of the time taken in eating is shown by the experiments on two men (K. B. and R. R.), each of whom ate ice cream at the same temperature (1.4 F.). K. B. ate the ice cream in 2.06 minutes, and had a decrease in gastric temperature of 20 F. and a recovery time of 46.8 minutes. R. R. ate the ice cream in 5.52 minutes, and had a decrease in gastric temperature of 8.6 F. and a recovery time of 37.3 minutes.

The apparent influence of the temperature of the ice cream is shown by the experiments on two women (B. B. and A. J.), each of whom required approximately the same time (1.96 and 1.98 minutes, respectively) to ingest the ice cream. B. B. ate ice cream having a temperature of 17.6 F., and had a decrease in gastric temperature of

2.6 F. and a recovery time of 24.2 minutes. A. J. ate ice cream having a temperature of 13.3 F., and had a decrease in gastric temperature of 14.9 F. and a recovery time of 30.7 minutes.

The apparent influence of the subject is shown by the experiments on two other women (A. S. and A. B.), each of whom ate ice cream having a temperature of 6.8 F. in approximately the same time (3.02 and 3 minutes, respectively). A. S. had a drop in gastric temperature of 8.8 F. and a recovery time of 42.5 minutes; A. B., a drop in gastric temperature of 12.5 F. and a recovery time of 26.3 minutes.

Apparently the decrease in gastric temperature was not governed by the amount of ice cream ingested. This is shown by the following experiments on 2 subjects, a man and a woman, each of whom was accustomed to eating large amounts of ice cream. Each subject performed the routine experiment on ice cream, and, in addition, on a later date, ingested several standard portions at one sitting. The man ate 90 Gm. (temperature, 6.8 F.) in 1.81 minutes; the decrease in gastric temperature was 43.8 F. and the recovery time, 40.3 minutes. He ate 540 Gm. (temperature 14 F.) in 9 minutes; the decrease in gastric temperature was 24.1. He insisted on changing his position after eating the ice cream, and this caused the loss of the test meal by emesis; therefore the recovery time could not be obtained. The woman ate 90 Gm. (temperature, 6.8 F.) in 2.7 minutes; the decrease in gastric temperature was 7.2 F., and the recovery time, 48 minutes. She ate 450 Gm. (temperature, 12.2 F.) in 8.05 minutes; the decrease in gastric temperature was 13 F., and the recovery time, 97 minutes.

*Hot Coffee.*—In these experiments, the volume of a portion of coffee varied between 140 and 350 cc. Such variations actually occur in practice, between a small cup, on the one hand, and a mug, on the other. The maximum temperature at which coffee may be ingested without discomfort varies markedly with the subject; in a series of eleven experiments (seven on men and four on women), it was found to lie between 113 and 149 F. On ingestion of hot coffee, an immediate, marked increase in gastric temperature occurred, followed by a decrease at first rapid, then progressively slower; finally, the graph again became a straight line which recorded exactly the same temperature for at least 10 minutes. The final temperature of the stomach tended to be slightly higher than its initial temperature, the average difference between the two temperatures being 0.1 F. The time required to drink the coffee was from 0.18 to 4.12 minutes. The increase in gastric temperature ranged between 4.2 and 17 F., and the recovery time between 19.9 and 45 minutes, exceeding 30 minutes in seven experiments.

*Possible Effect of Cold Drinks on the Temperature of the Upper Part of the Intestine.*—In the earlier experiments on the temperature of the upper part of the intestine, the resistance thermometer was passed in the usual manner, and a roentgenograph was taken. A meal of barium sulphate, chilled as usual, was administered, and another roentgenograph was taken, the subject being in the prone position at each exposure. Then the thermometer was removed. If the thermometer had not been in the intestine, the experiment was discarded.

In a series of nineteen successful experiments of this type (nine on men and ten on women) a decrease in the temperature of the upper part of the intestine followed the ingestion of the meal of chilled barium sulphate. This decrease was as little as 2 F., and as great as 16 F. This distinct decrease was immediately followed by an equally distinct increase. The decrease doubtless was due to leakage of a portion of the meal through the pylorus about the thermometer tube. Such leakage is apparent on some of the roentgenographs.

#### INFLUENCE OF PHYSICAL THERAPY ON GASTRO-INTESTINAL TEMPERATURE

Study was made of the influence on visceral temperature of the following forms of physical therapy: ice bag, hot wet pack, hot water bag, electric pad, infra-red lamp and diathermy. In one series, each form was applied over the true epigastric region. In another series, each form except the hot wet pack was applied over the region of the upper part of the intestine. There were twelve gastric hot wet pack experiments, divided approximately equally between the two sexes. The other experiments included thirty-four on the stomach and thirty-one on the upper part of the intestine; they were divided approximately equally between the two sexes, and between the five forms of physical therapy.

Each subject was undressed and put to bed. The ice bag and the hot water bag were applied by nurses in the usual clinical fashion. The electric pad was of the "three heat" variety; it was placed in its linen cover and applied directly to the surface of the skin, and used at either the high or the medium heat. The infra-red lamp and the diathermy were applied by the licensed physical therapists of the hospital. For diathermy, the anterior plate ranged from 3 by 3 inches (7.6 by 7.6 cm.) to 4 by 9 inches (10.16 by 22.9 cm.), the posterior plate from 4 by 5 inches (10.16 by 12.7 cm.) to 7 by 10 inches (17.78 by 25.4 cm.); the milliamperage almost always varied during a single experiment, and was as low as 500 and as high as 2,900. For the hot wet pack, a hot wet bath towel was placed directly over the skin, and covered with a sheet of rubber dam, over which the electric pad was placed, usually at high heat.

Each agent was applied to the anterior surface of the body. The exact surface area to which the agent was applied was determined in each case by comparison at the bedside with the roentgenographs. With each form of physical therapy, application was made of the maximum heat (or cold with the ice bag) which the individual subject found comfortable.



In each experiment, a mercury thermometer was used to measure the skin temperature. The bulb of the thermometer was placed in the middle of the true epigastric region in the experiments on the stomach, and immediately over the position of the resistance thermometer in experiments on the upper part of the intestine. The bulb was fastened to the skin firmly by means of adhesive tape; the stem of the thermometer was parallel to the long axis of the body. The bulb and a portion of the stem were covered by any physical therapeutic agent applied to the body surface. The skin temperature was read and recorded prior to the application of the agent and at frequent intervals during the course of the experiment.

The maximum skin temperatures observed during the application of the various forms of heat therapy were: hot wet pack, 109.4 F.; hot water bag, 129.2; electric pad, 134.6; infra-red lamp, 136.4, and diathermy, 105.8. The minimum skin temperature observed during the application of the ice bag was 44.6 F.

The period of application of the physical therapeutic agent extended from 35 to 140 minutes, and exceeded an hour in all but eleven of the seventy-seven experiments.

No distinct and uniform tendency to produce either an increase or a decrease in visceral temperature was observed on the application of the hot wet pack, the hot water bag, the electric pad or the infra-red lamp.

On application of the ice bag, a distinct tendency existed for a decrease in the temperature of the stomach and of the upper part of the intestine. In one experiment, an ice bag was applied for 10 minutes to the anterior body surface over the sigmoid with the subject in the Sims position; it produced no appreciable change in the sigmoidal temperature.

On application of diathermy, the visceral temperature uniformly increased, the average increase being 1 F. One man was used in two different experiments on the influence of diathermy on duodenal temperature. In each experiment, the period of application was approximately an hour. In one experiment, the milliamperage was gradually increased from 1,000 to 2,900, and the duodenal temperature increased 1 F. In the other experiment, the milliamperage was kept constant at 1,600, and the duodenal temperature increased 1.2 F.

As stated before, the subjects were in the supine position, and the physical therapeutic agent applied to the anterior surface of the body, since this is the usual clinical procedure. However, one experiment was made with a subject in the prone position in order to bring the abdominal viscera closer to the agent. When in the supine position the subject had shown a slight increase (0.5 F.) in gastric temperature with a hot wet pack. In the prone position, with an electric pad at high heat, her gastric temperature increased by 0.2 F.

None of the observed changes in visceral temperature exceeded the maximum variation in gastric temperature during similar periods of time as reported previously.

#### FRACTIONAL GASTRIC ANALYSIS AFTER INGESTION OF ICE WATER

A series of experiments was made on men who had been used in the study of the effect of ice water on gastric temperature. Two fractional gastric analyses were made in each experiment, the test meal being given after emptying the stomach; a period of one or more days intervened between the two analyses. Prior to the one analysis, the usual Ewald test meal was given; the tap water had a temperature between 63.5 and 85 F. Prior to the other analysis, an Ewald test meal with ice water (temperature, from 33.8 to 37.4 F.) was used. In each analysis fractions were withdrawn at intervals of 15 minutes; titrations were made by the Töpfer method for free hydrochloric acid, combined hydrochloric acid and total acidity; a sample of 1 cc. and centinormal sodium hydroxide solution were used in each titration.

When ice water was used, the gastric emptying time of the subject was increased by 15 minutes in four experiments, and by 30 minutes in four experiments. No change in emptying time was found in one experiment. Ingestion of ice water exerted no uniform effect on either the maximum concentration of any of the forms of acidity or the time of occurrence of these maximum values. Therefore, the actual numerical results of the acidity determinations have been omitted.

#### SUMMARY AND CONCLUSIONS

A recording resistance thermometer has been used to measure temperatures in the gastro-intestinal tract. In a group of 257 healthy, active subjects, the gastric temperature was between 97.5 and 102.2 F., (average 99.3 F.) and tended to be approximately 1 degree higher than the oral temperature. In a group of 53 subjects, the temperature of the upper part of the intestine lay between 98 and 100.1 F. (average 99 F.), and was within 1 degree of the gastric temperature. In a group of 6 subjects, the sigmoidal temperature lay between 100.8 and 101.5 F. (average 101.2 F.), and was higher than the oral temperature by 2 degrees or more.

Ingestion of either ice water (250 cc.) or ice cream (90 Gm.) produced a marked decrease in gastric temperature, followed by a rise, at first quite rapid, then progressively slower. The average recovery time was in excess of one-half hour. Use of ice water in a test meal delayed the gastric emptying time by from 15 to 30 minutes.

Evidence was obtained that leakage of a cold beverage through the pylorus lowers the temperature of the upper part of the intestine by

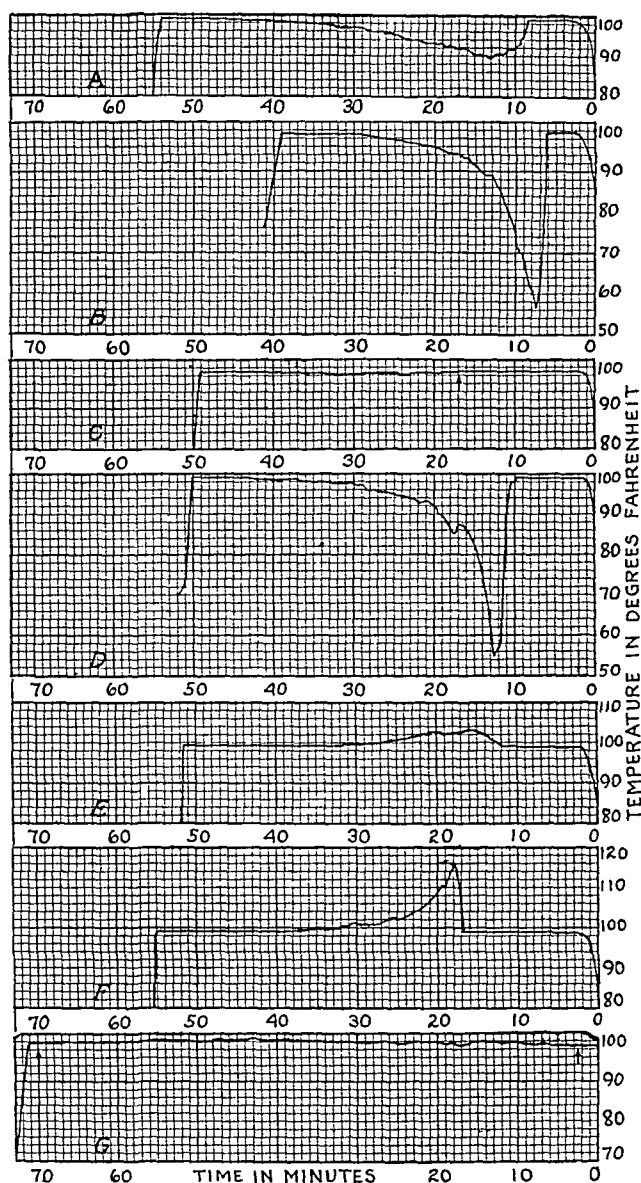


Fig. 2.—Changes in visceral temperature. Each graph is read from right to left. A rise in temperature at the right margin is due to swallowing. Graphs *A* to *F* record gastric temperature; graph *G*, duodenal temperature. Graph *A* records the minimum observed effect of ice water; graph *B*, the maximum observed effect of ice water; graph *C*, the minimum observed effect of ice cream (the arrow denotes beginning of ingestion); graph *D*, the maximum observed effect of ice cream; graph *E*, the minimum observed effect of hot coffee; graph *F*, the maximum observed effect of hot coffee; graph *G*, the maximum observed effect of any form of physical therapy. Diathermy was applied during the period between the arrows.

several degrees. This observation may throw light on the etiology of gastro-enteric disturbances in patients who have a rapid gastric emptying time and partake copiously of cold beverages.

Ingestion of hot coffee produced a marked increase (maximum increase, 17 F.) in gastric temperature, followed by a decrease, at first rapid, then progressively slower.

Physical therapeutic agents (electric pad, hot water bag, infra-red lamp, diathermy, hot wet pack and ice bag) were applied over either the stomach or the upper part of the intestine, usually for an hour or longer. None of the observed changes in visceral temperature exceeded the maximum variation in gastric temperature during similar periods of time in a control series.

The application of heat to the abdomen produces a feeling of comfort when localized or general pain exists. However, in view of the results obtained in this research, the production of any reparative benefit by local application of heat or cold is conjectural. It is doubtful that the benefit obtained is sufficient to warrant subjecting the patient to the various local applications of heat, especially in summer. Consultation with several physiologists has not produced any explanation of the process resulting in the feeling of comfort. The results also render debatable the use of ice locally for the control of gastric or intestinal hemorrhage, and the local application of heat to promote the healing of gastric or duodenal ulcer.

# CHANGES IN GASTRIC ACIDITY IN PEPTIC ULCER, CHOLECYSTITIS AND OTHER DISEASES

ANALYZED WITH THE HELP OF A NEW AND ACCURATE TECHNIC

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For fifty years the study of gastric acidity in disease has been hampered, first, by the absence of detailed standards of normal for persons of varying age and sex and, second, by a cumbersome method of classifying acidity, a method that tends to obscure any but large differences between two sets of data.

We recently published standards of normal based on the records of 3,746 persons. The reader is referred to that paper<sup>1</sup> for many details in regard to technic and other matters.

Our standards for free and total acidity and for the incidence of achlorhydria in adults will be found in table 1. So far as children and young persons aged less than 20 years are concerned (table 2), we can provide standards only for free acidity because our data were meager and unsatisfactory in regard to total acidity and the incidence of achlorhydria.

In our previous article we did not analyze the data regarding gastric content removed. We have now done this, and include the more important statistical constants in table 1.

## PLAN OF STUDY

For the purpose of this study we calculated for each diseased person in whom free acid was demonstrated the difference between his or her observed free acidity and the normal for a person of corresponding sex and age, and then took the mean of these differences as an index of the

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† Working on a grant from the Josiah Macy, Jr., Foundation.

✓1. Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, J.: The Normal Range of Gastric Acidity from Youth to Old Age: An Analysis of 3,746 Records, *Arch. Int. Med.* **49**:345 (March) 1932.

deviation from normal of all the patients with the particular disease under consideration. A similar procedure was carried out in determining the difference from normal of the total acidity and the volume of gastric contents removed.

It should be noted that here again, just as during the study of normal persons, we have not averaged in the readings of persons lacking free acid. Instead we have compared the percentage incidence of achlorhydria in each five-year group with the normal incidence for that group, and have then averaged these differences so as to obtain the mean deviation from normal of the whole group. For convenience in comparison we have expressed this difference also as a percentage of the

TABLE 1.—*Normal Standards for Free and Total Acidity, Volume and Achlorhydria of Adults\**

Age	Males								Females							
	Free Acid, Units		Total Acid, Units		Volume, Cc.		Achlorhydria, per Cent		Free Acid, Units		Total Acid, Units		Volume, Cc.		Achlorhydria, per Cent	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	True	Apparent	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	True	Apparent
24-29.....	46.7	16.5	63.5	16.5	118.0	49.5	....	....	32.0	14.5	49.7	14.5	100.5	39.0	2.0	3.0
25-29.....	47.0	17.0	63.0	16.2	116.5	50.5	....	2.0	33.0	14.0	50.0	14.2	100.0	39.0	4.5	6.5
30-34.....	47.0	16.7	62.5	16.2	113.5	50.0	3.0	5.2	33.0	13.7	50.5	14.7	99.0	39.0	7.3	10.0
35-39.....	47.0	16.5	61.7	16.4	109.5	48.5	6.3	8.5	33.0	14.0	50.5	15.1	97.7	39.0	10.0	13.5
40-44.....	46.5	16.5	60.7	17.2	105.0	46.0	9.5	11.7	33.0	13.8	50.5	15.2	96.0	39.0	12.7	17.0
45-49.....	45.5	16.7	59.5	18.4	101.0	43.0	12.7	15.0	33.0	13.5	50.5	14.2	94.0	38.5	14.5	20.5
50-54.....	43.7	17.6	58.3	19.1	97.5	41.0	16.0	18.5	33.0	14.0	50.5	14.7	92.0	37.5	18.2	24.0
55-59.....	41.5	18.7	57.0	19.2	95.0	42.0	19.3	21.5	33.5	15.0	50.5	15.3	89.5	37.0	21.0	27.5
60-64.....	39.3	19.4	55.5	18.8	93.5	45.0	22.0	25.0	33.5	16.0	50.5	16.0	87.0	36.0	23.5	31.0
65-69.....	37.3	18.5	53.7	17.5	92.0	47.0	22.5	26.0	33.5	16.0	50.5	16.7	84.0	35.0	26.3	31.5
70-79.....	33.5	17.0	50.5	16.7	91.0	50.5	17.0	21.0	33.5	15.2	50.5	17.2	79.0	33.0	24.0	28.7

\* The mean values given in this table are different from those given in our previous publication (Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, J.: *Arch. Int. Med.* 49: 345 [March] 1932) by a constant correction.

incidence of achlorhydria that would be expected in a group of normal persons with a similar age distribution. An example of the arithmetic used in the several processes mentioned is given in an appendix at the end of the paper.

The test meal employed at the Mayo Clinic is of the Ewald type, and consists of 8 arrowroot cookies and 400 cc. of water. After one hour a sample of gastric contents is removed with the small Sawyer tube; it is tested for free acid and if this is present the stomach is emptied and the tube is withdrawn. If, however, there is no free acid, the tube is left in and three more samples are removed at intervals of fifteen minutes. The results of titration are expressed in the usual terms of cubic centimeters of tenth-normal sodium hydroxide required to neutralize 100 cc. of gastric juice.

In the work on normal standards, and also in this paper, we have in every case used the figures for free acid obtained at the end of the first hour. The only use made of subsequent readings with the fractional test has been to help in distinguishing between what we call true and apparent achlorhydria. By true achlorhydria we mean a condition in which none of the several fractions removed in the course of the second hour showed free acid; by apparent achlorhydria we mean a condition in which the first sample did not show free acid but later samples did.

We do not wish at this point to enter into any controversy as to the number of these cases of achlorhydria in which on repeated tests, or with the stimulus of histamine, free acid might have been shown. We

TABLE 2.—*Normal Standards for Free Acid in Children and Youths\**

Age, Years	Males		Females	
	Mean	Standard Deviation	Mean	Standard Deviation
1.....	6.5	7.3	4.0	8.4
2.....	12.0	8.0	9.0	8.8
3.....	17.0	8.5	13.0	9.2
4.....	20.5	9.0	16.0	9.6
5.....	23.0	9.6	18.5	10.0
6.....	24.5	10.2	20.5	10.5
7.....	26.0	10.8	21.8	11.0
8.....	26.5	11.3	23.0	11.4
9.....	27.0	11.7	23.5	11.8
10.....	27.5	12.0	24.0	12.2
11.....	27.5	12.5	24.3	12.5
12.....	28.0	13.0	24.5	12.9
13.....	30.0	13.5	24.8	13.4
14.....	33.0	14.0	25.0	13.7
15.....	37.0	14.5	26.0	14.0
16.....	41.5	14.9	26.5	14.2
17.....	44.5	15.2	28.0	14.4
18.....	45.5	15.5	29.0	14.6
19.....	45.8	15.7	30.0	14.6
20.....	46.0	16.0	31.3	14.6

\* Expressed in clinical units.

are simply reporting the number of cases in which free acid was not demonstrated with the type of test meal which we used.

Because of the uncertainty in regard to the amount of dilution which occurs when the pylorus is blocked, we have omitted from consideration cases in which there was gastric retention, as evidenced by the presence of food residue or of a volume of gastric contents larger than 250 cc.

It is obvious that two distributions may differ not only as regards the value of the mean but also as regards the spread or range of the data; hence it is necessary to compare not only the means but also the standard deviations which give a measure of the spread. Actually in these studies the standard deviations of the data from the several groups of diseased persons were not found to differ significantly from normal, except in a few instances in which they were slightly decreased. Because the variations from normal were so small, the actual figures will not be pub-

lished. The fact that they did not vary from normal indicates simply that when a disease is associated with a variation in gastric acidity, each individual in the group is affected in the same way and to about the same degree.

Although we studied both free and total acidity, the figures for total acidity followed so closely those found in the case of free acidity that it did not seem worth while to publish them.

#### CHANGES IN ACIDITY ASSOCIATED WITH DUODENAL ULCER

We have studied records of gastric analysis in the cases of 1,495 men and 398 women with duodenal ulcer. The diagnosis was verified at

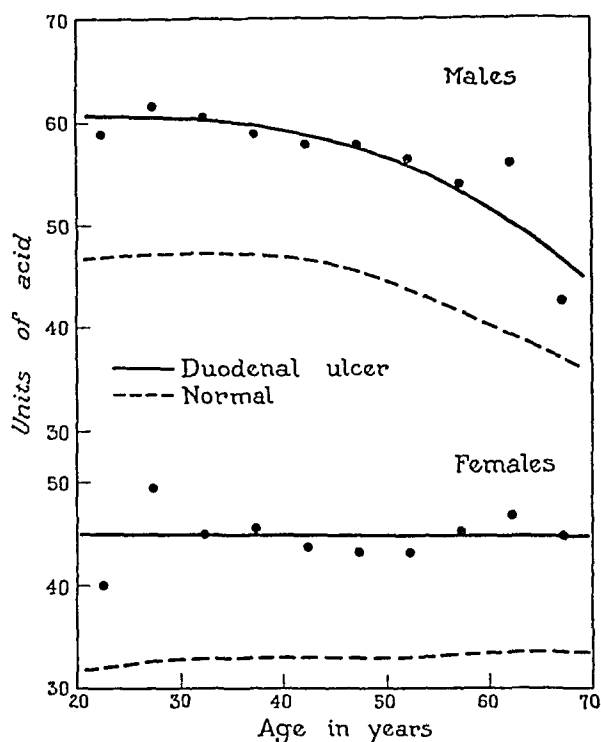


Fig. 1.—Dots indicate mean free acidity for duodenal ulcer in males and in females for each five year age group. Solid lines represent the regression of these points with age. The dotted lines indicate the level of mean acidity in normal persons.

operation on 1,357 of the men and 343 of the women. In the remaining few cases there was a typical clinical history and a definite deformity of the duodenal cap.

As every one knows, duodenal ulcer is commonly associated with an increase in gastric acidity. In our series the mean increase among men was 12.3 units and among women, 11.5 units. Figure 1 brings out the interesting fact that when the figures expressing mean acidity for men and women of different ages were plotted, the curve representing gastric secretion in cases of ulcer was found to be parallel to that representing secretion in normal persons, but it had been shifted upward a distance



corresponding to about 12 units. Apparently, then, these curves represent some biologic variation with age which is so deeply rooted that it is not easily eradicated in disease.

In 13 of the cases of ulcer there was no free acid in the sample of gastric contents removed at the end of an hour, but in 10 of these, later specimens did reveal some free acid. As one of us (Dr. Eusterman<sup>2</sup>) and Palmer<sup>3</sup> have shown, the complete absence of free acid is extremely rare in the presence of duodenal ulcer.

*Acidity in the Presence of Severe Symptoms.*—In order to see if there was any difference in acidity in the case of patients with mild and severe symptoms of ulcer, we divided the data into two groups: one derived from the study of patients who could easily be treated medically, and the other from patients who had to be operated on. In the men who had been treated medically, the mean free acidity averaged only 7.1 units higher than normal as contrasted with an increase of 12.8

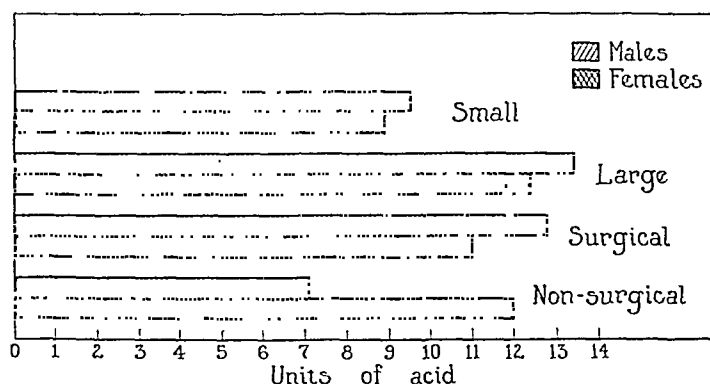


Fig. 2.—The lower two bars represent the mean increases of free acid above normal in the case of duodenal ulcers which were treated by surgical and nonsurgical measures. The upper bars represent the increased acidity present in the case of ulcers larger than 5 mm., contrasted with that present in the case of smaller ulcers.

units in the men who required operation (fig. 2). There was almost no difference between the mean acidities of the two groups of women.

Of the patients who were treated surgically, 431 had a perforating type of ulcer, while 946 had shallow lesions. No significant difference could be demonstrated between the mean gastric acidities in these two groups, but the patients with small single lesions had from 2 to 3 units less acidity than those with large or multiple lesions.

The volume of gastric contents removed from patients with duodenal ulcer was increased over the normal by an average of 10 cc. This

2. Eusterman, G. B.: Achlorhydria: Practical Consideration of Its Clinical Significance, *Northwest Med.* **30**:249 (June) 1931.

3. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcer: I. Achlorhydria, *Arch. Int. Med.* **38**:603 (Nov.) 1926.

increase was slightly less marked among patients with single small ulcers, and in the case of the men with ulcers which were treated medically the mean volume was somewhat less than normal.

The smallness of the increase in volume (10 cc.) of the gastric juice removed is remarkable when one remembers that it has always been taught that duodenal ulcer produces marked hypersecretion and delay in the final emptying of the stomach. It is to be recalled, however, that all cases in which there was definite retention were omitted from the study.

#### CHANGES OF ACIDITY IN GASTRIC ULCER

In spite of the difficulties which are inherent in the old cumbersome method of summarizing data obtained by gastric analysis, it has been fairly clear to many physicians in the past that the acidity in cases of

TABLE 3.—*Deviations from the Normal in Gastric Ulcer in Men and Women*

Disease	Free Acid, Volume												
	Age, Years			Mean Difference in Units of Acid		Mean Difference, Cc.		Achlorhydria					
								True Difference, per Cent			Apparent Difference, per Cent		
								Mean	Probable Error	Percentage of Normal	Mean	Probable Error	Percentage of Normal
	Patients	Mean	Standard Deviation	Mean	Probable Error	Mean	Probable Error						
Gastric ulcers—total group	188	44.8	12.0	−5.7	1.2	+14.6	3.0	−6.5	2.3	46	−4.0	2.5	75
Large ulcers.....	116	50.1	7.9	−6.0	1.0	+12.9	3.0	−9.8	3.1	26	−8.8	3.3	43
Small ulcers.....	54	49.9	5.2	−5.4	1.3	+16.1	4.2	−7.4	4.5	43	−3.3	4.9	80
Ulcers in proximal third..	58	43.9	18.0	−7.9	1.4	+7.1	4.1	−9.3	4.2	23	−3.3	4.6	80
Ulcers in middle third.....	66	48.7	8.2	−4.8	1.5	+20.4	3.4	−10.0	4.0	17	−7.6	4.3	50
Ulcers in distal third.....	32	48.6	10.5	−3.1	1.6	+35.5	6.2	−10.5	6.0	23	−10.2	6.4	38

gastric ulcer is usually not so high as in cases of duodenal ulcer. Several writers have stated that the acidity in cases of gastric ulcer is not different from normal, but so far as we know, no one has ever recognized the fact that it is lower than normal. So far as achlorhydria is concerned, the impression that we gained from reviewing the literature is that it is present just as often in patients with ulcer of the stomach as in normal persons.

In order that there might be no error in our figures ascribable to mistakes in diagnosis, we selected for analysis the figures for acidity obtained in the case of 160 men and 28 women, in all of whom a gastric ulcer was demonstrated at operation. We excluded data for all patients with gastric stasis due to mechanical obstruction at the pylorus.

In the case of the patients with gastric ulcer the mean free acidity was reduced by an average of 5.4 units in men and 6.6 units in women. Apparent achlorhydria was frequently noted, especially in the case of men, in whom the incidence was only 22 per cent less than normal.

Both men and women had true achlorhydria only half as often as normal. The volume of gastric juice removed at the end of an hour was increased on the average 13.1 cc. in men and 16.6 cc. in women.

Because we wished to see if the size of the lesion had anything to do with the degree of reduction in acidity, we divided the data into two groups: one from patients with lesions less than 5 mm. in diameter, and the other from patients with larger ulcers. Because of the small numbers of cases, the data from men and women were combined. There

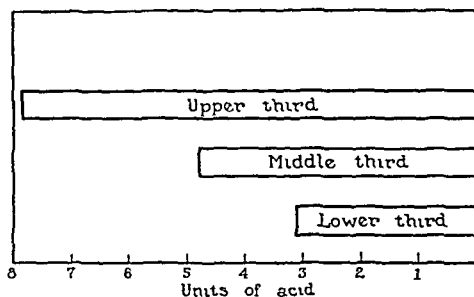


Fig. 3.—The bars show the decreases of mean free acidity below normal in gastric ulcers situated in the upper, middle and lower thirds of the stomach.

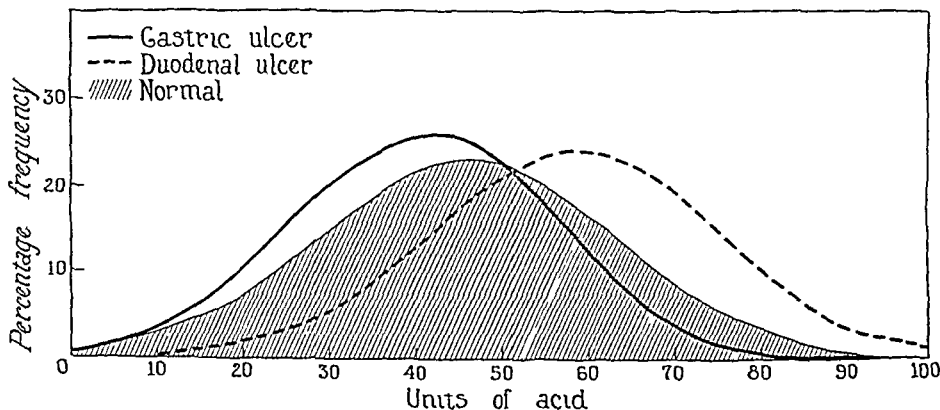


Fig. 4.—Percentage distribution curve for free acidity in males. The gastric ulcer and duodenal ulcer curves give the percentage occurrence of free acids in these groups. The shaded area gives the percentage occurrence for a group of normal persons of the same ages. It is to be noted that both pathologic groups overlap considerably with each other and with the normal, although their means are significantly different.

appeared to be a slightly greater reduction in acidity with the larger ulcers, but the difference was not great enough to be convincing.

We next looked for differences in acidity corresponding to differences in the situation of the ulcer in the stomach, and an interesting gradation was found. Ulcers at or near the pylorus were associated with acid values which were not significantly different from the normal. With ulcers in the middle third of the stomach the acidity was reduced

by 4.8 units, while with ulcers in the upper third it was reduced by 7.9 units (fig. 3 and table 3). A similar observation was made years ago by Smithies.<sup>4</sup>

As was to be expected, although the acidity of the secretion was affected to a greater degree with lesions high in the stomach than with lesions near the pylorus, the reverse was true with respect to the volume of secretion. Ulcers near the pylorus increased the volume by 35.5 cc., those in the middle third increased it by 20.4 cc. and those in the upper third had no effect on it.

It is obvious, then, that gastric acidity in cases of ulcer of the stomach and of ulcer of the duodenum is altered from the normal in opposite directions (fig. 4). Several hypotheses might be advanced to explain this fact, but any theorizing at this time would be of so little value that we shall not attempt it.

#### MEAN GASTRIC ACIDITY IN THE PRESENCE OF GASTRO- JEJUNAL ULCER

Gastric acidity is usually lowered by gastro-enterostomy, but when in an occasional case a jejunal ulcer forms, it is commonly assumed that the acids of the stomach have remained high.

For the purposes of this study we analyzed data from 174 men and 14 women with an anastomotic ulcer demonstrated surgically. The mean free acid was less than normal among the men by 3.7 units and among the women by 10.8 units. When it is remembered that these patients had all been operated on previously for duodenal ulcer, in which condition the acidity is usually high, it is apparent that a great lowering in mean acidity had occurred since operation. Among the men this loss must have averaged 16.5 units and among the women, 22.2 units.

None of the 14 women had achlorhydria, but some of the men did. Among them the incidence of this peculiarity was not so high as among normal persons, but it was many times higher than that of patients with duodenal ulcer. This does not mean necessarily that the stomachs of these persons were incapable of secreting acid, but perhaps only that during the time when the test was being made the acid formed was being neutralized as fast as it was secreted.

The amount of gastric secretion removed from the stomachs of men at the end of an hour was practically the same as in the case of duodenal ulcer. Among the women the increase was three times this, or about 30 cc., but the group was so small that this observation cannot be stressed.

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4. Smithies, Frank: Gastric Ulcer Without Food Retention: A Clinical Analysis of One Hundred and Forty Operatively Demonstrated Cases, *Am. J. M. Sc.* **145**:340 (March) 1913.

## CAN ONE DETECT A SETTING FOR GASTROJEJUNAL ULCER?

In the case of 50 of the patients with gastrojejunal ulcer, all men, we had a record of the gastric acidity present before gastro-enterostomy. The mean free acidity of these patients was 12.5 units above normal, which is almost exactly the figure that was found in patients with duodenal ulcer who were treated surgically. In no instance was there achlorhydria. The volume of gastric secretion was increased by 15.6 cc., which is 4 cc. more than the increase in the group of patients with duodenal ulcer severe enough to require operation.

The only conclusion possible from this study of gastric acidity of patients who submitted to gastro-enterostomy for the relief of duodenal ulcer is that there is no difference in mean gastric acidity in the two groups of cases in which jejunal ulcer develops later, and in those in which it does not. In other words, there is no warrant for the commonly held belief that one can, by measuring gastric acidity, recognize those cases of duodenal ulcer in which gastro-enterostomy is likely to be followed by the development of gastrojejunal ulcer.

The fact that studies of the gastric acidity have failed to help us at this point has not discouraged us from continuing to look for significant peculiarities in other constituents of the gastric juice, such as pepsin.

## EFFECT OF CHOLECYSTITIS ON MEAN GASTRIC ACIDITY

The impression gained from the voluminous literature on the subject is that cholelithiasis and acute cholecystitis may cause an increase in gastric acidity, whereas chronic cholecystitis is frequently associated with subacidity or achlorhydria. Some investigators, however, have concluded that there is no significant change in gastric acidity in cases of cholecystitis.

For the purposes of this study we took records from 602 cases in which the diagnosis of cholecystitis, with and without stones, was confirmed at operation. In both groups the mean free acidity was not significantly different from normal in either men or women. Neither was there any difference in the volume of secretion such as would indicate that there is commonly a change in the emptying time of the stomach. There was, however, a slight increase in the incidence of achlorhydria of men.

✓ *Cholecystectomy.*—Meyer, Ivy and McEnergy<sup>5</sup> found in experimental animals that cholecystectomy commonly produced slight hypersecretion, but no definite evidence of this has been found in the case of man. Hartman and Rivers<sup>6</sup> were unable to show any constant alteration, but

5. Meyer, Jacob; Ivy, A. C., and McEnergy, E. T.: The Effect of Cholecystectomy on Gastric Secretion, *Arch. Int. Med.* **34**:129 (July) 1924.

6. Hartman, H. R., and Rivers, A. B.: The Effect of Cholecystectomy on Gastric Acidity, *Ann. Int. Med.* **1**:558 (Feb.) 1928.

we thought it worth while to reinvestigate the problem with the new and more accurate method of statistical analysis. In this study we used records from the cases of 59 men and 118 women. The interval between cholecystectomy and gastric analysis varied from a few months to several years. In the case of men there was a lowering of mean free acid by about 4 units, but this could not be shown in the case of the women. There were curious changes from normal in the incidence of achlorhydria, but on account of the small size of the groups their significance is doubtful.

*Cholecystitis in Association With Duodenal Ulcer.*—Cholecystitis and duodenal ulcer are so commonly associated that we wished to know what effect the combination would have on gastric acidity. For purposes of analysis we took records from the cases of 125 men and 89 women. All of the patients had been operated on for duodenal ulcer, and all of them had either submitted to cholecystectomy or were found to be suffering from cholecystitis at the time of operation for ulcer. In these cases free acid was increased by 13.3 units in the men and by 12.6 units in the women. These figures are approximately 1 unit higher than in the case of surgical duodenal ulcer alone. The volume of secretion was normal in the men and greatly increased in the women.

#### ALLERGY

In a recent article Bray<sup>7</sup> published his observations on a group of 200 asthmatic children in whom he found gastric acidity markedly lower than normal, and the frequency of achlorhydria increased. He suggested that with the lowering of digestive power in the stomach there might be an increase in absorption of incompletely split proteins which, in turn, might sensitize the patient and produce the asthma.

Little is known about the gastric acidity of adults suffering from allergic types of disease, but the general impression is that there is a lessening in the amount of acid. We observed 34 men and 43 women who suffered from various conditions such as urticaria, angioneurotic edema and asthma. The mean acidity of the men was lower than normal by 3.6 units; that of the women was higher than normal by 3.4 units. On account of the smallness of the groups these differences cannot be considered significant. The incidence of achlorhydria was slightly less than expected, but again the difference was not large enough to be significant.

There seems to be little doubt about the lowering of gastric acidity of children with asthma. On comparing Bray's published data with our standards of normal the mean free acid was found to be lowered by 9.6 units.

7. Bray, G. W.: Hypochlorhydria of Asthma in Childhood, *Quart. J. Med.* 24:181 (Jan.) 1931.

TABLE 4.—*Deviations from Normal in Various Diseases*

Disease	Pa- tients	Achlorhydria										
		Age, Years	Free Acid		Volume		True		Apparent			
			Standard Devia- tion	Mean Difference in Units of Acid		Mean Difference, Cc.	Difference in per Cent		Difference in per Cent			
				Mean	Probable Error		Mean	Probable Cent of Error Normal	Mean	Probable Cent of Error Normal		
Mean	Mean	Men	Mean	Probable Error	Mean	Probable Cent of Error Normal	Mean	Probable Cent of Error Normal	Mean	Probable Cent of Error Normal		
Duodenal ulcer, total group.....	1,495	42.5	10.8	+12.3	0.2*	+10.8	1.5*	-9.3	0.7*	-11.4	0.8*	10
Medically treated.....	138	45.4	11.7	+7.1	1.0*	-3.0	2.2	-10.6	2.6*	-12.7	2.8*	13
Surgically treated.....	1,357	42.3	10.7	+12.8	0.3*	+11.6	1.6*	-9.1	0.8*	-11.2	0.9*	10
Penetrating type of ulcer.....	431	43.3	11.4	+13.3	0.6*	+12.7	1.7*	.....	.....	.....	.....	.....
Shallow ulcers.....	926	42.6	10.5	+12.6	0.4*	+11.1	1.5*	.....	.....	.....	.....	.....
Multiple ulcers.....	167	41.2	10.1	+13.4	0.9*	+13.2	2.7*	.....	.....	.....	.....	.....
Single large ulcers.....	188	42.1	9.7	+13.4	2.6*	+10.5	2.6*	.....	.....	.....	.....	.....
Single small ulcers.....	87	40.0	9.0	+10.5	1.2*	+4.0	3.2	.....	.....	.....	.....	.....
Developed jejunal ulcer later.....	50	39.2	13.2	+12.5	1.3*	+15.4	3.0*	.....	.....	.....	.....	.....
Gastrojejunal ulcer.....	174	41.6	10.1	-3.7	1.0*	+10.1	3.3*	-2.1	2.2	-1.5	2.4	86
Gastric ulcer, total group.....	160	44.3	12.3	-5.4	0.9*	+16.6	2.6*	-6.0	2.4	-2.9	2.6	78
Cholecystitis.....	95	44.8	11.7	-2.8	1.2	+0.1	3.0	+2.9	3.1	+3.7	3.4	127
Cholelithiasis.....	86	48.8	10.2	+0.7	2.2	+1.6	4.8	+1.7	3.6	+1.6	3.9	110
Postcholecystectomy.....	59	51.0	11.7	-4.2	1.5*	+6.1	3.4	-4.1	6.4	+3.6	6.9	121
Cholecystitis and duodenal ulcer.....	123	44.3	10.6	+13.3	1.1*	+0.3	2.8	-9.8	2.5*	-12.0	2.8*	1
Allergic disease.....	34	42.5	13.4	-3.6	1.9	.....	.....	-0.6	4.8	-2.6	5.3	78
Migraine.....	97	40.3	10.1	-0.7	1.2	-4.6	2.7	-4.5	2.8	-4.4	3.1	55
Psychoneurosis.....	185	39.5	11.7	+1.3	0.9	-10.6	2.2*	+4.1	1.9	+4.0	2.2	140
Chronic nervous exhaustion.....	339	40.4	10.8	+0.6	0.6	+7.7	2.0*	+1.9	1.5	0.0	1.7	100
Women												
Duodenal ulcer, total group.....	443	44.3	10.4	+11.1	0.6*	+14.3	1.6*	-12.7	1.6*	-16.6	1.8*	12
Medically treated.....	100	44.6	8.7	+11.0	1.2*	+10.5	2.8*	-13.0	3.3*	-16.5	3.6*	11
Surgically treated.....	343	44.2	10.6	+11.4	0.6*	+15.3	1.8*	-12.4	1.8*	-16.6	2.0*	12
Penetrating type of ulcer.....	74	46.6	11.3	+10.9	1.1*	+22.7	3.6*	.....	.....	.....	.....	.....
Shallow ulcers.....	260	43.4	10.6	+11.6	0.6*	+13.2	2.0*	.....	.....	.....	.....	.....
Multiple ulcers.....	39	41.4	9.7	+11.5	1.2*	+1.7	2.5	.....	.....	.....	.....	.....
Single large ulcers.....	52	40.3	14.1	+12.4	1.4*	+10.0	2.1*	.....	.....	.....	.....	.....
Single small ulcers.....	39	45.7	16.0	+8.9	1.3*	+9.7	4.3	.....	.....	.....	.....	.....
Gastrojejunal ulcer.....	14	41.5	10.2	-10.8	2.3*	+25.0	7.3*	.....	.....	.....	.....	0
Gastric ulcer, total group.....	28	47.7	10.5	-6.6	1.8*	-1.2	4.5	-8.4	6.8	-9.9	7.5	46
Cholecystitis.....	224	43.3	10.0	-0.6	0.6	+3.1	2.1	-0.5	2.2	-1.4	2.5	92
Cholelithiasis.....	197	46.7	11.3	-0.3	0.7	-1.3	1.1	-2.3	2.5	-3.5	2.8	82
Postcholecystectomy.....	118	45.9	11.2	-0.2	0.9	.....	.....	-0.2	3.2	-3.7	3.5	78
Cholecystitis and duodenal ulcer.....	89	46.8	10.7	+12.6	1.1*	+33.9	3.5*	-15.1	3.8*	-20.3	4.1*	0
Allergic disease.....	43	39.1	13.2	+3.4	1.5	.....	.....	-1.6	4.5	-0.7	5.2	95
Migraine.....	140	40.8	10.0	+2.4	0.8*	+0.5	.....	0.0	2.8	-1.7	3.1	90
Psychoneurosis.....	156	42.2	12.3	+1.0	0.8	-4.1	2.3	+0.8	2.6	+0.5	2.9	100
Chronic nervous exhaustion.....	535	42.3	11.8	-0.8	0.4	-2.2	1.3	-2.5	1.4	-3.6	1.6	78

\* Probable error is less than one-third the corresponding mean value, indicating that this value is statistically significant.

## MIGRAINE

Migraine is of great interest to the gastro-enterologist because it so often produces nausea and vomiting and gastric stasis. We observed 97 men and 140 women in all of whom a gastric analysis was made during the interval between headaches. The mean free acid of the men was 0.7 units below normal, and the incidence of achlorhydria was half the normal one. The mean free acid of the women was increased by 2.4 units and the incidence of achlorhydria was normal. The volume of gastric secretion was apparently normal.

Our impression is that none of the slight differences found is clinically significant.

## PSYCHONEUROSIS AND CHRONIC NERVOUS EXHAUSTION

One hundred years ago Beaumont<sup>8</sup> noticed that anger caused a drying of the gastric mucosa in the case of Alexis St. Martin. Since then many observations have been made, all indicating that anxiety and painful emotion can produce marked inhibition of gastric secretion and motility. There are reports in the literature of lower acidity in patients suffering from melancholia. Most of these patients were confined to asylums and therefore must have been much more seriously affected than were our patients who came of their own accord to the clinic. There were 186 men and 156 women, all of whom were suffering with a psychoneurosis, usually of the anxiety type. In addition to the patients with psychoneurosis there were 337 men and 535 women suffering with chronic nervous exhaustion, and showing symptoms of emotional instability. In both groups the mean free acid of the men was slightly but not significantly higher than normal. Among the women there was practically no difference from the normal.

Among the men with psychoneurosis the incidence of achlorhydria was increased by 58 per cent, and among men with nervous exhaustion it was increased by 22 per cent. On the other hand, among women with psychoneurosis the incidence of achlorhydria was normal, and among those with chronic nervous exhaustion it was 20 per cent below normal. These observations are hard to understand and in view of the large probable error their significance is questionable. In none of the groups was there any significant difference from normal in the volume of gastric contents.

## COMMENT

We believe that the new method of analyzing gastric acidity in disease has several advantages over the old. First, we use more detailed standards of normal; second, we express a deviation from normal in

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8. Beaumont, William: *The Physiology of Digestion With Experiments on the Gastric Juice*, ed. 2, Burlington, Vt., Chauncy Goodrich, 1847.



simpler terms; third, we can estimate the degree of reliability of any deviation found, and fourth, we can study the degree of overlapping of the distribution curve representing data from diseased persons with the normal curve.

The first three advantages have been stressed in the introduction to the paper. The amount of overlapping of the distribution curves for gastric and duodenal ulcer is shown in figure 4. There it will be seen that even when, as in the case of duodenal ulcer or gastric ulcer, there is a definite shift in the value of the mean, there is still only a small group of cases in which the results of a gastric analysis can have any great diagnostic value. Actually the range of normal is so great that no reading can be pathognomonic of any disease. All one can say is that the probabilities are small or large that a gastric or duodenal ulcer is present.

It should be noted that we have not said that duodenal or gastric ulcer caused a change in acidity; instead we have been careful to say merely that the disease was associated with an increase or decrease in acid values. So far as we can see, our data do not throw any light on the old problem of whether a duodenal ulcer causes hyperacidity, or whether the presence of hyperacidity leads to the formation of an ulcer.

#### SUMMARY

There was an increase of approximately 12 units of free acidity in the case of duodenal ulcer, an increase which varied with the size of the ulcer, with the number found at operation and with the severity of the symptoms produced. Less than 1 per cent of the patients with duodenal ulcer failed to show free acid after an Ewald test meal.

In 50 cases studied, the gastric acidity of patients with duodenal ulcer who, after gastro-enterostomy, returned with jejunal ulcer was not higher than that of patients similarly operated on who, after two or more years, are still free from symptoms of jejunal ulcer.

In 174 men with gastro-jejunal ulcer, the mean free acidity was lower than normal by about 4 units. The incidence of true achlorhydria was 71 per cent of normal.

In the case of gastric ulcer the mean free acidity was lower than normal by about 6 units. This lowering was more marked in the cases of ulcers situated in the proximal two thirds of the stomach. The incidence of achlorhydria was half of that observed in normal persons.

Practically no change from normal was found in the mean free acidity of patients with cholecystitis and cholelithiasis. No change from normal could be found in the gastric acidity of patients who had submitted to cholecystectomy. In the case of patients who suffered with a combination of disease of the gallbladder and ulcer of the duodenum, the acidity was slightly higher than in the case of patients with uncomplicated duodenal ulcer.

There was no significant deviation from normal in the mean gastric acidity of patients suffering with allergic manifestations, migraine, psychoneurosis and chronic nervous exhaustion. Among the men with a psychoneurosis the incidence of achlorhydria was increased about 50 per cent and among those with migraine it was decreased about 50 per cent. In both groups the incidence of achlorhydria among women was normal.

In the absence of marked organic obstruction at the pylorus it was noted that with duodenal ulcer and gastrojejunal ulcer there was a slight increase in the amount of gastric juice removed; there was also a slight increase in the presence of gastric ulcers situated in the distal two thirds of the stomach.

#### APPENDIX

*Methods of Comparing the Results of Gastric Analysis in a Group of Diseased Persons With Those in a Normal Group of the Same Age and Sex Composition.*—So far as concerns gastric acidity and volume recovered, a simple procedure is to express the reading of each patient as a deviation, in actual units, from the mean value of the normal standard for the patient's sex and age. These differences, plus and minus, are then added algebraically and an average obtained. If the group being studied is normal as to gastric acidity or volume, as the case may be, this average will be zero or will not differ significantly in a statistical sense from zero. To know whether a given difference is significant, we must know its probable error; if it is less than three times its probable error it is customary to consider it "not significant." For the particular mean difference with which we deal here, obtained from a standard that varies with every age, the formula for the probable error is not explicitly presented in any statistical reference. However, it may be calculated straightforwardly from elementary statistical theorems. Here space forbids us to present the algebraic derivations, but the results of the analysis together with an example of the arithmetical process used are given. In these examples it will be seen that we do not actually set up each individual difference to obtain an average, but that a more summary method is used. It is to be understood that precisely the same results are obtained as would be by the longer process. On a similar principle the percentage of persons with achlorhydria found in a diseased group is compared with a normal group of the same age and sex.

In tables 5 and 6, capital letters are used to represent functions of the standard group, and small letters functions of the diseased group. An  $n$  represents the number of persons in a group studied;  $M$  and  $m$  represent means;  $\Sigma$  and  $\sigma$ , standard deviations;  $D$ , a difference, and P. E., the probable error. In table 6,  $n_a$  represents the number in the diseased group with achlorhydria, and  $P$  and  $p$  represent percentages

Following are examples of calculation in a group of psychoneurotic women.

TABLE 5.—Free Acidity\*

Age, Years	n	M	Σ	m	σ	n × M	n × m	n × Σ	n × σ	σ <sup>2</sup>	n × σ <sup>2</sup>
20-24	9	32.0	14.5	28.4	13.5	288.0	255.6	130.5	121.5	182.25	1,640.25
25-29	15	33.0	14.0	35.2	14.6	495.0	528.0	210.0	219.0	213.15	3,179.40
30-34	22	33.0	13.7	33.0	13.3	726.0	726.0	301.4	292.6	176.89	3,891.58
35-39	22	33.0	14.0	26.7	13.3	726.0	587.4	303.0	292.6	176.89	3,891.58
40-44	10	33.0	13.8	35.0	13.0	330.0	350.0	138.0	130.0	169.00	1,690.00
45-49	15	33.0	13.5	35.9	13.8	495.0	538.5	202.5	207.0	190.44	2,856.60
50-54	20	33.0	14.0	29.6	12.8	660.0	592.0	280.0	256.0	163.84	3,276.80
55-59	7	33.5	15.0	35.4	13.5	234.5	247.8	105.0	94.5	182.25	1,275.75
60-64	8	33.5	16.0	30.8	8.4	268.0	246.4	138.0	67.2	70.56	564.48
65-69	2	33.5	16.0	45.0	11.0	67.0	90.0	32.0	22.0	121.00	242.00
130						4,289.5	4,181.7	1,835.4	1,702.4		22,526.44

\* Total volume is treated similarly.

In example 1 (table 5),  $M_M = \frac{4,289.5}{130} = 32.996$ . The weighted mean acidity of the comparable normal group.

$M_m = \frac{4,181.7}{130} = 32.166$ . The weighted mean acidity of the diseased group.

$D_m = 32.166 - 32.996 = -0.830$ . The weighted mean difference from the normal standard.

$\sigma_{D_m} = \frac{\sqrt{22,526.44}}{130} = 1.1545$ . Standard deviation of  $D_m$ .

$P.E._{D_m} = 0.6745 \times 1.1545 = 0.7787$ . Probable error of  $D_m$ . (In this example the probable error is almost as large as the difference and hence this difference is not statistically significant.)

For the purpose of comparing the spread of the data in the diseased and normal groups we must compute the standard deviations.

$M_\Sigma = \frac{1,835.4}{130} = 14.118$ . The weighted mean standard deviation of the comparable normal group.

$M_\sigma = \frac{1,702.4}{130} = 13.095$ . The weighted mean standard deviation of the diseased group.

$D_\sigma = 13.095 - 14.118 = -1.023$ . The weighted mean difference between the standard deviations of the two groups.

$\sigma_{D_\sigma} = \sqrt{\frac{22,526.44}{2 \times 130}} = 0.9816$ . Standard deviation of  $D_\sigma$ .

$P.E._{D_\sigma} = 0.6745 \times 0.9816 = 0.66$ . Probable error of  $D_\sigma$ .

TABLE 6.—*True Achlorhydria*

Age, Years	n	n <sub>1</sub>	P	n × P	P × (100-P)	n × P(100-P)
20-24....	11	2	2.0	22.0	196.00	2,156.00
25-29....	15	0	4.5	67.5	429.75	6,446.25
30-34....	25	2	7.3	182.5	676.71	16,917.75
35-39....	25	3	10.0	250.0	900.00	22,500.00
40-44....	13	3	12.7	165.1	1,108.71	14,413.23
45-49....	18	2	15.5	279.0	1,309.75	23,575.50
50-54....	24	2	18.2	436.8	1,488.76	35,730.24
55-59....	11	3	21.2	231.0	1,679.00	18,249.00
60-64....	10	2	23.5	235.0	1,797.75	17,977.50
65-69....	4	2	26.3	105.2	1,938.31	7,753.24
	156	21		1,974.1		165,718.71

In example 2 (table 6),  $M_r = \frac{1,974.1}{156} = 12.654$ . Weighted mean percentage representing the incidence of achlorhydria in the comparable normal group.

$M_p = \frac{21}{156} \times 100 = 13.461$ . Weighted mean percentage representing the incidence of achlorhydria in the diseased groups.

$D_p = 13.461 - 12.654 = 0.807$ . The weighted mean difference in the percentage of achlorhydria from the normal standard.

$$\sigma_{D_p} = \frac{\sqrt{165,718.71}}{156} = 2.61. \text{ Standard deviation of } D_p.$$

$$PE_{D_p} = 0.6745 \times 2.61 = 1.76. \text{ Probable error of } D_p.$$

# NITROGEN AND SULPHUR METABOLISM IN BRIGHT'S DISEASE

## IV. RETENTION OF UREA IN THE NEPHROSIS SYNDROME

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It has previously been noted by Peters and others<sup>1</sup> that patients exhibiting the nephrosis syndrome retain a large proportion of the intake of nitrogen without an increase in the nonprotein nitrogen in the blood, and that even when crystalline urea is added to the diet, it is retained. Peters and Van Slyke<sup>2</sup> thought that the retention of nitrogen serves to make up the loss of body protein chiefly in the form of albumin excreted in the urine. If this is true, it accounts in part for the retention of sulphur noted formerly.<sup>3</sup> So far as I have been able to ascertain, no studies have been made on the relation between the excretion of nitrogen and that of sulphur in this condition when crystalline urea has been added to a diet already high in protein. I shall report metabolism studies on a patient, whose case history was included in the first paper of this series (case 4).<sup>3</sup> It is sufficient to state that she presented a picture typical of lipoid nephrosis (nephrosis syndrome). The significant criteria are given in table 1. The period of study was thirty-six consecutive days, from Feb. 23 to March 31, 1928. On April 1, the patient contracted a fulminating infection, and she died four days later. Her condition during the entire period of study was essentially stationary, and so far as could be determined, the outward evidences of edema did not change. It will be noted in the accompanying chart that she gained slightly in weight despite the diuresis; the entire variation, however, was within about 10 per cent of her weight on admission.

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From the Medical Clinic of the Peter Bent Brigham Hospital.

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1. Peters, J. P.; Bulger, H. A.; Lee, Carter, and Murphy, C. F.: The Relation of Albuminuria to Protein Requirement in Nephritis, *Arch. Int. Med.* **37**:153 (Feb.) 1926. Rabinowitch, I. M., and Childs, M. C. C.: A Contribution to the Biochemistry and Treatment of Chronic Nephrosis (Epstein), *ibid.* **32**:758 (Nov.) 1923. Peters, J. P., and Moor, D. D.: *J. Clin. Investigation* **6**:5, 1928.

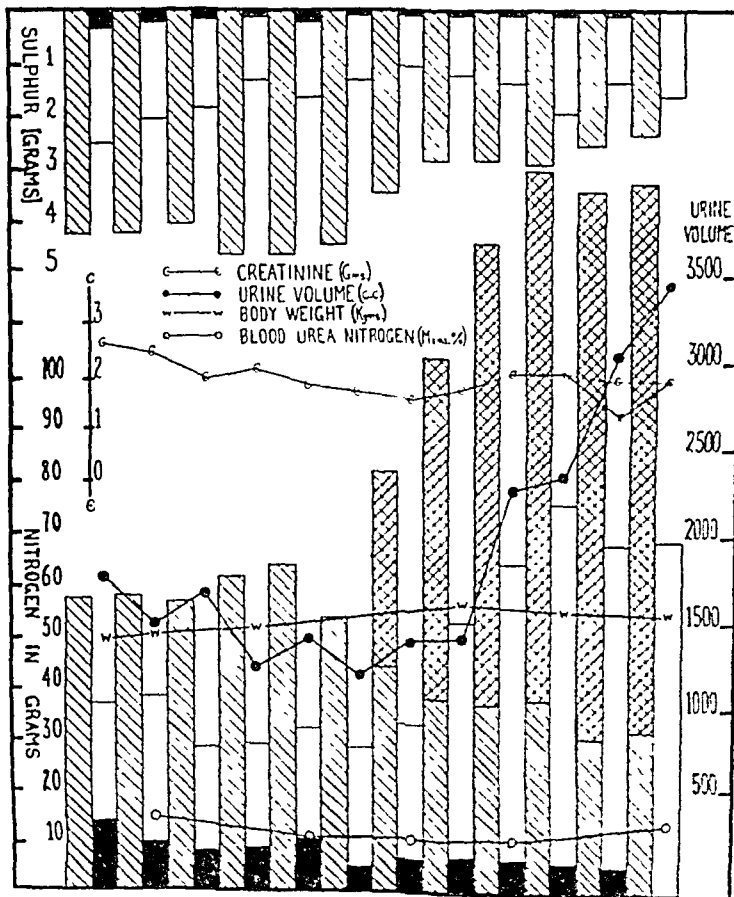
2. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

3. Grabfield, G. P.: *J. Clin. Investigation* **9**:311, 1930.

The chart represents the study in twelve consecutive three day periods. The diet was weighed, and the food refused was weighed. The total intake of fluid was kept constant at 2,500 cc. per day. this figure including the fluid in the food. The food was not analyzed, but standard tables of composition were used. The accompanying chart

TABLE 1.—*Significant Laboratory Findings in Case 4 During the Period of Study*

Date	Phthalein Excretion, Percentage in 2 <sup>10</sup> '	Total Plasma Protein, Percentage	Serum Albumin, Percentage	Serum Globulin, Percentage	Blood Cholesterol, Mg. per 100 Cc.	Blood Urea Nitrogen, Mg. per 100 Cc.
February 13.....	70	....	....	....	...	11
February 14.....	..	4.01	0.97	3.04	246	..
February 25.....	..	....	....	....	...	15
March 5.....	..	3.44	0.52	2.92	180	11
March 12.....	..	....	....	....	471	11
March 19.....	..	3.92	0.47	3.45	...	11



The nitrogen and sulphur metabolism in case 4 graphically depicted, with other significant findings over a consecutive thirty-six day period. Each double column represents a three day period. The solid black columns represent the output of nitrogen or sulphur in albumin; the diagonally crossed columns, the intake of nitrogen or sulphur in food; the white columns, the output of nitrogen or sulphur; the cross-hatched columns, the intake of nitrogen as urea.

presents the pertinent data; the diagonally crossed and cross-hatched columns represent the intake; the black and the white columns, the output. It should be emphasized that the figures represent nitrogen and sulphur, and not protein or urea. The black portions of the columns for excretion represent the output of nitrogen or of sulphur as albumin. The total albumin was determined by the sulphosalicylic acid method, and the sulphur was calculated as for serum albumin, which contains 1.8 per cent according to Hammarsten's figures. Creatinine was determined as a check on the urinary collections, and it will be seen that this curve runs essentially constant. In the eleventh period, all the figures are corrected as indicated in the creatinine<sup>3a</sup> curve because it was known that some urine was unavoidably lost.

The whole study may be conveniently divided into two periods: eighteen days with urea and eighteen days without urea (table 2). The

TABLE 2.—*Summary of the Figures Shown on the Chart*

	Period I, 18 Days	Period II, 18 Days
Intake of nitrogen, Gm. ....	354.0	726.0
Output of nitrogen (urine), Gm. ....	192.0	333.0
Nitrogen retained, Gm. ....	162.0	373.0
Intake of sulphur, Gm. ....	26.0	16.7
Output of sulphur, Gm. ....	10.5	8.3
Sulphur retained, Gm. ....	15.5	8.4
Nitrogen : sulphur ratios:		
Urine .....	18.3	42.5
Intake .....	13.6	43.5
Intake, excluding 506 Gm. of crystalline urea.....	13.6	13.2
Retained .....	10.4	44.5

preurea period indicates what has been so often observed in patients with the nephrosis syndrome, namely, a strongly positive nitrogen and sulphur balance amounting to the retention of large quantities of both substances. It is interesting to study a little more closely the relationship between the nitrogen and the sulphur in these two periods. It will be seen that in both periods the ratio of nitrogen to sulphur in the food ingested was 13:1, whereas in the output during the first period the ratio was 18:1. It is evident, therefore, that during the first period more sulphur was retained than nitrogen, and the ratio of nitrogen to sulphur retained was 10:1. In the second period, if one takes into account the total intake of nitrogen minus the output, the ratio is 45:1. If, on the other hand, one considers that all the nitrogen in the urine in the second period came from urea, and that only the protein nitrogen of the diet was retained, the ratio is 26:1. It is evident,

3a. The feces were not analyzed as previous studies have shown that no significant change is made in the results by the fecal nitrogen or sulphur.

therefore, that there is some alteration in the mechanism of the retention of nitrogen and sulphur brought about by the exhibition of large quantities of urea. It is obvious that the sulphur in the urine must come from the breakdown of body or food protein, as the urea contains none. It is obvious, furthermore, from the figures given that some of the crystalline urea is retained in the body. Not only was the total urinary excretion of nitrogen less than the urea nitrogen administered, but if it is assumed that the protein behaved as it did in the preurea period and that the ratio of nitrogen to sulphur in the protein retained was 10:1, the retention of nitrogen from the dietary protein in the second eighteen days would be 124 Gm., which is considerably more than is reasonable from the total figures. It is interesting to note that the excretion of sulphur was slightly greater during the period urea was being administered than during the preurea period, compared with the intake; that is, during the first period almost 60 per cent of the intake of sulphur was retained, whereas in the second period 50 per cent was retained. This difference is possibly not significant; it is merely noted in passing.

The important question centers around the fate of the retained nitrogen. The patient studied was one whose plasma proteins were tremendously depleted, in whom the albumin-globulin ratio was reversed, and who, despite the diet high in protein and the urea, was apparently unable to repair the loss of plasma protein nitrogen. There is some evidence that with a tremendously high intake of urea there is a diminution in the output of nitrogen as albumin, but there is no evidence of regeneration of plasma protein. As to the fate of the retained nitrogen, I can offer no explanation. It obviously does not appear in the blood as nonprotein nitrogen. The quantities that are retained represent nearly 2 Gm. per hundred cubic centimeters of fluid in the entire body, if the body is considered as being 85 per cent composed of fluid. If the retained urea in such patients remains diffusible, it is inconceivable that this would not have been detected in the figures for the urea nitrogen of the blood, which, it will be seen, remained constant and low. The possibility of the storage of all this nitrogen somewhat after the manner of deposit protein is conceivable, though the quantity far exceeds the figures heretofore reported.

During the period urea was being administered, the retention of nitrogen, calculated as "flesh," would amount to  $373 \times 6.25 \times 4$ , or 9.3 Kg. During this period the weight remained essentially constant, and the diuresis amounted to about 6,000 cc. over and above the preceding level of the urinary output. Therefore, approximately 3 Kg. of tissue has to be accounted for. Unfortunately on the first day of the administration of urea the weight was not recorded, and it may be that the gain shown on the chart, amounting to about 3 Kg., occurred



in that period. In any case, these figures are sufficiently suggestive to make the hypothesis of Van Slyke, that nitrogenous products are retained as "flesh," the likely one. Apparently, judging by these two periods, the body will retain the sulphur-rich moiety of the protein molecule if it is available, but will retain a protein of low sulphur content if only that is available. The significant fact is that this is an indication (though by no means proof) that under conditions such as exist in this patient urea may be converted into protein.

That the whole picture may concern the question of deposit protein and an anomaly of protein metabolism is further emphasized by the analogy between such patients and patients with hypothyroidism, which has been frequently mentioned in the literature. It is striking that in myxedematous persons after the administration of thyroid substance<sup>4</sup> and in normal persons on the administration of iodides,<sup>5</sup> the extra nitrogen that first appears in the urine comes from the sulphur-poor moiety of the protein molecule, indicating that the body in each of these situations holds on most strongly to the sulphur-rich protein. In nephrosis the urinary nitrogen-sulphur ratio is high. These data are reported as an indication of the metabolic problem.

#### SUMMARY

1. The excretion of nitrogen and sulphur has been studied for a thirty-six day period in a patient exhibiting the nephrosis syndrome.

2. During half of this time, crystalline urea in large quantities was added to the diet. This produced diuresis.

3. Definite evidence is given that crystalline urea is retained but does not appear in the nonprotein nitrogen of the blood.

4. It is suggested that the retained nitrogen is stored as "flesh," possibly to replace the deposit protein which has been called on to maintain the serum proteins lost through the kidneys.

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4. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Sloose, J.: *Tr. A. Am. Physicians* **40**:195, 1925.

5. Grabfield, G. P.: *Boston M. & S. J.* **197**:1121, 1927.

# UREA CLEARANCE TEST IN PREGNANCY

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The studies of Van Slyke and his associates<sup>1</sup> have established on a firm foundation the relation between the concentration of urea in the blood and that in the urine of normal persons under a variety of conditions. As a result of these and of similar investigations, it is generally recognized that the urea clearance test is perhaps the most reliable method available for the quantitative estimation of renal functional efficiency. Certain factors have been shown to affect the rate of removal of urea from the blood of normal persons. As demonstrated by Addis and Drury,<sup>2</sup> MacKay<sup>3</sup> and Van Slyke, Alving and Rose,<sup>4</sup> severe exercise may diminish urea clearance somewhat, presumably by diverting an unduly large proportion of blood to muscular tissues, with a resulting diminution in the renal circulation. Moderate exercise, however, as shown by Van Slyke, Alvin and Rose<sup>4</sup> and by Bruger and Mosenthal,<sup>5</sup> has no significant influence on the blood urea clearance. The relation-

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1. (a) Van Slyke, D. D.; McIntosh, J. F.; Möller, E.; Hannon, R. R., and Johnston, C.: Studies of Urea Excretion: VI. Comparison of the Blood Urea Clearance with Other Measures of Renal Function, *J. Clin. Investigation* **8**:357, 1930; (b) Austin, J. H.; Stillman, E., and Van Slyke, D. D.: Factors Governing the Excretion Rate of Urea, *J. Biol. Chem.* **46**:91, 1921; (c) Möller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J. Clin. Investigation* **6**:427, 1928; (d) III. The Influence of Body Size on Urea Output, *ibid.* **6**:467, 1928.

2. Addis, T., and Drury, D. R.: The Rate of Urea Excretion: VII. Effect of Various Other Factors than Blood Urea Concentration on the Rate of Urea Excretion, *J. Biol. Chem.* **55**:629, 1923.

3. MacKay, E. M.: Studies of Urea Excretion: V. The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease, *J. Clin. Investigation* **6**:505, 1928.

4. Van Slyke, D. D.; Alving, A., and Rose, W. C.: Studies of Urea Excretion: VII. The Effects of Posture and Exercise on Urea Excretion, *J. Clin. Investigation* **11**:1053, 1932.

5. Bruger, M., and Mosenthal, H. O.: Urea Clearance Test as an Index of Renal Function: I. Studies of Normal Subjects, *Arch. Int. Med.* **50**:351 (Sept.) 1932; II. The Effect of Ingestion of Carbohydrate (Dextrose), *ibid.* **50**:359 (Sept.) 1932.

ship between the weight of the kidneys, the area of the body surface and the renal function has been demonstrated by Taylor, Drury and Addis,<sup>6</sup> MacKay and Raulston,<sup>7</sup> MacKay,<sup>8</sup> Addis,<sup>9</sup> Addis, Myers and Oliver<sup>10</sup> and Möller, McIntosh and Van Slyke.<sup>11</sup> It has been found that the urea clearance and the weight of the kidneys are proportional to the area of the body surface. Addis and Drury<sup>2</sup> and Addis, Barnett and Shevsky<sup>11</sup> found that the urea clearance was increased by caffeine and small doses of epinephrine and was decreased by solution of pituitary and large doses of epinephrine. As stated by Peters and Van Slyke,<sup>12</sup> these factors may cause variation in the blood urea clearance either by altering the minute flow of blood through the kidneys or by so influencing the activity of the renal cells that variations occur in the percentage of urea removed from the blood at each passage.

There are comparatively few reports of the employment of the urea clearance test for the determination of renal functional efficiency during pregnancy. Stander, Ashton and Cadden,<sup>13</sup> for four normal women, who were stated to be near term, obtained values ranging from 92 to 110 per cent of the average normal; for three women with "low reserve kidney" the figures ranged from 62 to 122 per cent; for nine with nephritis complicating pregnancy the figures varied from 55.5 to 94 per cent. A more extensive series was studied by Hurwitz and Ohler.<sup>14</sup> For five normal pregnant women they obtained figures of from 83 to 161 per cent; the duration of pregnancy was not stated. Abnormally low values were obtained for fourteen of seventeen women with chronic nephritis, for five with eclampsia and for eight of twenty-one with other forms

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6. Taylor, F. B.; Drury, D. R., and Addis, T.: The Regulation of Renal Activity: VIII. The Relation Between the Rate of Urea Excretion and the Size of the Kidneys, *Am. J. Physiol.* **65**:55, 1923.

7. MacKay, E. M., and Raulston, B. O.: Factors Which Determine Renal Weight; Renal Function, *J. Exper. Med.* **53**:109, 1931.

8. (a) MacKay, E. M.: Comparison of Relation Between Rate of Urea Excretion and Amount of Renal Tissue in Dog and Other Mammals, *Am. J. Physiol.* **100**:402, 1932; (b) Kidney Weight, Body Size and Renal Function, *Arch. Int. Med.* **50**:590 (Oct.) 1932.

9. Addis, T.: Renal Lesion in Bright's Disease, *Am. J. M. Sc.* **176**:624, 1928.

10. Addis, T.; Myers, B. A., and Oliver, J.: The Regulation of Renal Activity, *Arch. Int. Med.* **34**:243 (Aug.) 1924.

11. Addis, T.; Barnett, G. D., and Shevsky, A. E.: The Regulation of Renal Activity: I. Regulation of Urea Excretion by the Concentration of Urea in the Blood and in the Urine, *Am. J. Physiol.* **46**:1, 1918.

12. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry (Interpretations)*, Baltimore, Williams & Wilkins Company, 1931, p. 350.

13. Stander, H. J.; Ashton, P., and Cadden, J. F.: The Value of the Various Kidney Function Tests in the Differentiation of the Toxemias of Pregnancy, *Am. J. Obst. & Gynec.* **23**:461, 1932.

14. Hurwitz, D., and Ohler, W. R.: Urea Clearance Test in Toxemias of Pregnancy, *J. Clin. Investigation* **11**:1119, 1932.

of toxemia of pregnancy. In view of the grave prognostic significance of nephritis occurring as a complication of pregnancy and because of the reliance placed on the urea clearance test in the early detection of renal functional impairment, this study was undertaken to determine whether or not the blood urea clearance in the pregnant state differs from that in the normal nonpregnant state.

The report is based on tests made on forty-seven pregnant women, of whom thirty-nine showed a normal condition, seven had chronic glomerulonephritis and one had myocardial failure. The determinations of urea clearance were made in most cases in the last two months of gestation, the exact time being noted in the tables; as therein indicated, a few determinations were made during the puerperal period. The technic employed in the performance of the test was that advocated by Möller, McIntosh and Van Slyke,<sup>1c</sup> with the exception that, in view of the difficulty of otherwise insuring the complete emptying of the bladder, all specimens of urine were obtained by catheterization. Determinations of urea in the blood and urine were made by the urease-aeration method of Van Slyke and Cullen,<sup>15</sup> the determinations of urea in the blood being made with the Benedict (1932) filtrate. As advocated by Möller, McIntosh and Van Slyke,<sup>1c</sup> the test period was from 8 to 10 a. m. Correction by taking into account the area of the body surface was made according to their suggestion.

#### EXPERIMENTAL DATA

The detailed findings with regard to the urea clearance test are presented in tables 1 and 4. The thirty-nine patients included in the normal group showed no clinical or laboratory evidence of disease (except the urea clearance findings). The majority of those studied at term had been carefully observed in the antenatal clinic for several months prior to their admission to the hospital. Seven patients in the abnormal group presented definite clinical and laboratory evidence of chronic glomerulonephritis, and one was suffering from myocardial failure, with a moderate degree of generalized edema.

In the normal group, the blood urea clearance, in terms of percentage of the average normal (54 cc., standard clearance and 75 cc., maximum clearance), varied from 28 to 184. As indicated in table 2, there appeared to be a remarkably close relationship between the number of months of pregnancy that had elapsed when the test was made and the urea clearance values, the latter showing a distinct tendency to diminish as the pregnancy progressed. Following delivery, values of 62, 117 and 184 per cent were obtained in three cases. The same rela-

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15. Van Slyke, D. D., and Cullen, G. E.: The Determination of Urea by the Urease Method, *J. Biol. Chem.* **24**:117, 1916.

TABLE 1.—*Urea Clearance in Thirty-Nine Cases of Normal Pregnancy*

Patient	Month of Gestation	Blood Urea N, Mg. per 100.Cc.	Urine Volume, Cc. per Min.	Urea Clearance, Per Cent of Normal
A. D.....	3	6.66	0.8	120
A. McG.....	4	8.63	0.53	112
E. L.....	3	11.11	2.41	110
E. K.....	3	8.24	1.1	103
I. S.....	5	15.7	0.81	100
	9	11.95	0.56	29
	2 days post partum	8.98	1.1	62
R. S.....	5	8.24	0.33	100
A. S.....	6	10.27	0.4	100
F. B.....	6	11.11	0.56	100
A. C.....	6	10.27	0.6	96
J. R.....	7	13.33	0.7	90
E. M.....	7	14.28	0.58	89
M. R.....	7	15.78	0.75	88
D. L.....	9	10.79	2.5	88
S. McD.....	9	14.49	2.2	87
E. M.....	9	13.57	1.36	85
C. E.....	9	11.45	1.5	82
A. F.....	8	14.7	0.34	79
R. E.....	8	8.92	0.37	75
M. G.....	9	10.90	0.43	75
A. D.....	9	15.87	0.75	74
C. B.....	7	13.04	0.6	72
	9	19.35	0.72	66
L. H.....	9	16.39	0.31	68
T. P.....	9	8.82	0.95	66
H. M.....	9	14.18	0.35	66
L. B.....	9	10.79	0.45	64
S. B.....	9	9.9	0.34	64
N. Di P.....	6	15.0	0.69	64
	8	14.28	0.6	61
	9	12.24	1.1	30
L. C.....	9	14.42	0.41	61
	2 days post partum	14.28	0.54	117
E. M.....	9	9.93	0.7	53
E. M.....	9	10.24	0.92	53
M. O.....	7	12.39	1.25	50
	9	12.0	0.18	31
R. G.....	9	12.29	1.23	50
S. H.....	9	10.13	1.15	50
D. J.....	9	9.61	0.35	48
B. W.....	9	11.32	1.75	46
F. K.....	9	11.45	0.76	40
D. K.....	9	9.8	0.6	28
A. W.....	2 days post partum	9.2	2.08	184
A. K.....	9	14.49	0.33	59

TABLE 2.—*Average Values of Urea Clearance in Different Months of Normal Pregnancy*

Month of Gestation	Number of Cases	Urea Clearance, Per Cent of Normal	Average Urea Clearance
3.....	3	103-120	111
4.....	1	112	112
5.....	2	100	100
6.....	4	64-100	90
7.....	5	50-90	78
8.....	3	61-79	72
9.....	25	28-88	59
Post partum.....	3	62-184	121

tionship appeared to be maintained in five cases in which determinations were made at different periods in pregnancy, as illustrated in table 3.

In the abnormal group, the urea clearance values ranged from 20 to 51 per cent in the seven patients with chronic glomerulonephritis, and a figure of 70 per cent was obtained for one patient with myocardial failure and generalized edema.

TABLE 3.—*Urea Clearance at Different Periods of Gestation in Five Patients*

Patient	Percentage of Normal at Given Month of Gestation					Percentage of Normal Post Partum
	5	6	7	8	9	
I. S. ....	100	..	..	..	29	62
O. B. ....	..	..	72	..	66	..
N. Di P. ....	..	64	..	61	30	..
L. C. ....	..	..	..	..	61	117
M. O. ....	..	..	50	..	31	..

TABLE 4.—*Urea Clearance in Seven Cases of Chronic Glomerulonephritis and One of Myocardial Failure Complicating Pregnancy*

Patient	Month of Gestation	Blood Urea N, Mg. per 100 Cc.	Urine Volume, Cc. per Min.	Urea Clearance, Per Cent of Normal	Condition
E. McC.	4	13.51	0.31	40	Chronic glomerulonephritis
L. D.	Three days post partum	14.15	0.41	40	Chronic glomerulonephritis
E. E.	4½ months after abortion	11.07	0.33	51	Chronic glomerulonephritis
M. G.	8	20.68	0.62	37	Chronic glomerulonephritis
B. W.	6	27.02	0.58	70	Myocardial failure, with generalized edema
T. B.	9	13.21	1.7	27	Chronic glomerulonephritis
L. B.	6	10.6	1.83	20	Chronic glomerulonephritis
E. O'N.	9	7.42	0.42	20	Chronic glomerulonephritis

## COMMENT

Möller, McIntosh and Van Slyke<sup>1c</sup> found the lower limit of the normal variation of standard blood urea clearance to be about 75 per cent, and that of maximum clearance to be about 85 per cent of the average normal values. Since practically all the patients in this series had urine volumes of less than 2 cc. per minute, the calculations being made on the basis of the standard clearance formula, 75 per cent may be considered as representing the lower limit of normal for this group. Bruger and Mosenthal<sup>5</sup> stated that single determinations as low as 52 per cent may at times be obtained in normal subjects, but we have never observed this degree of variation in normal persons studied under standard conditions. Our experience is in accord with that of Van Slyke and his associates, who believe that in the majority of instances the most reliable results are obtained if the urea clearance values are interpreted in terms of deviation from the average normal rather than if individual determinations are considered as lying within the probable

range of normal variation. However, in the absence of any other evidence of renal functional impairment, as emphasized by Bruger and Mosenthal,<sup>5</sup> minor variations should not be interpreted dogmatically as absolute values of renal functional efficiency.

If 75 per cent is considered the lower limit of normal for this group of normal pregnant women, twenty patients, or 52.6 per cent, must be considered as showing evidence of renal functional impairment. Values of 50 per cent or less were obtained in nine cases (23.6 per cent). However, as stated previously, in no instance was there any other indication of renal dysfunction, all of the women studied at term passing through an essentially normal labor and puerperal period so far as other than local conditions were concerned. Furthermore, observations showed a gradual decrease in blood urea clearance as pregnancy progressed, with essentially normal findings in the first six to seven months, a rather marked diminution in many cases at term and a sudden increase in the early days of the puerperium. In view of these observations, it is difficult to escape the conviction that the subnormal values which may occur during pregnancy, particularly just prior to the onset of labor, are dependent on factors other than actual renal functional impairment. Our findings are at variance with those of Hurwitz and Ohler,<sup>14</sup> who, in five normal cases, observed no values below 83 per cent, and with those of Stander, Ashton and Cadden,<sup>13</sup> who, in four cases, obtained values of from 93 to 110 per cent. However, their normal cases were obviously too few in number to warrant any definite conclusion, and, particularly in the case of the former, no exact statement was made as to the point in the period of gestation at which the studies were made.

It has long been recognized that normal pregnancy is associated with distinct alterations in protein metabolism and nitrogen balance. The early work of Hagemann,<sup>16</sup> of Jägerroos,<sup>17</sup> of Murlin<sup>18</sup> and of Zacharjewski<sup>19</sup> demonstrated that the early months of pregnancy are associated with a negative, and the latter months, particularly the last two, with a distinctly positive nitrogen balance. As shown by Slemons,<sup>20</sup> during the early days of the puerperium the previously positive nitrogen balance suddenly becomes negative. Occasionally a negative nitrogen balance may be observed during the few days preceding

16. Hagemann, O.: Inaug. Dissert., Berlin, 1891.

17. Jägerroos, B. H.: Studien über den Eiweiss-, Phosphor- und Salzumsatz während der Gravidität, *Arch. f. Gynäk.* **66**:517, 1902.

18. Murlin, J. R.: Metabolism of Development: III. Qualitative Effects of Pregnancy on the Protein Metabolism of the Dog, *Am. J. Physiol.* **28**:422, 1911.

19. Zacharjewski, A. U.: Ueber den Stickstoffwechsel während der letzten Tage der Schwangerschaft und der ersten Tage des Wochenbettes, *Ztschr. f. Biol.* **12**:368, 1893-1894.

20. Slemons, J. M.: Metabolism in Pregnancy, *Johns Hopkins Hosp. Rep.* **12**:121, 1904.

delivery, which is probably the result of failing appetite and possibly of beginning catabolic changes, as Stander<sup>21</sup> states. Several observers, including Killian and Sherwin,<sup>22</sup> Caldwell and Lyle,<sup>23</sup> de Wesselow<sup>24</sup> and Stander,<sup>21</sup> have noted a moderate decrease in the concentration of urea in the blood during pregnancy. It has been our experience that the blood urea nitrogen tends to diminish, particularly in the last few months of gestation. Furthermore, Murlin and Bailey<sup>25</sup> found that the relative proportion as well as the absolute amount of urinary urea was diminished in pregnancy, probably as a result of protein retention, which is most marked in the later months.

Other changes occur during pregnancy which may affect the quantitative elimination of urea by the urine. An extremely variable and usually progressively increasing quantity of urea is present in the amniotic fluid. Williams and Bargaen<sup>26</sup> found that the concentration of urea nitrogen in the amniotic fluid averaged about 18.25 mg. per hundred cubic centimeters, the total nonprotein nitrogen being about 27.05 mg. per hundred cubic centimeters; similar findings were obtained by Cantarow, Stuckert and Davis.<sup>27</sup> The effect on maternal urea elimination of this accumulation of urea in a fluid of unknown origin can only be conjectured, but it must be accepted as representing an additional point of difference between protein metabolism in the pregnant and in the nonpregnant state.

It is well recognized that the elimination of urea by the urine is influenced by the rate and volume of blood flow through the kidneys. It appears probable that marked alteration in this important function may occur during pregnancy in consequence of the tremendous and progressive increase in the vascularity of the pelvic organs. Finally, another important factor must be taken into consideration, namely, the increase in total and basal metabolism which occurs during the last half of pregnancy. This subject has been carefully studied by a number of investigators, whose work has been summarized by DuBois.<sup>28</sup> The

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21. Stander, H. J.: *Toxemias of Pregnancy*, Medicine **8**:1, 1929.

22. Killian, J. A., and Sherwin, C. P.: *Some Chemical Studies in Normal and Abnormal Pregnancies*, Am. J. Obst. & Gynec. **2**:6, 1921.

23. Caldwell, W. E., and Lyle, W. G.: *The Blood Chemistry in Normal and Abnormal Pregnancy*, Am. J. Obst. & Gynec. **2**:17, 1921.

24. de Wesselow, O. L. V.: *Some Chemical Observations on the Toxemias of Pregnancy*, J. Obst. & Gynaec. Brit. Emp. **29**:21, 1922.

25. Murlin, J. R., and Bailey, H. C.: *Further Observations on the Protein Metabolism of Normal Pregnancy*, Arch. Int. Med. **12**:288 (Sept.) 1913.

26. Williams, J. L., and Bargaen, J. A.: *The Uric Acid Content of Human Amniotic Fluid*, Am. J. Obst. & Gynec. **7**:406, 1924.

27. Cantarow, A.; Stuckert, H., and Davis, R. C.: *The Chemical Composition of Amniotic Fluid: Comparative Study of Human Amniotic Fluid and Maternal Blood*, Surg., Gynec. & Obst. **57**:63 (July) 1933.

28. DuBois, E. F.: *Basal Metabolism in Health and Disease*, Philadelphia, Lea & Febiger, 1927.



alteration in basal metabolism results from a number of factors, including the development of the fetus, placenta and uterus, changes in body weight and the increased intra-abdominal pressure which adds to the labor of respiration. A number of observers believe that the increase in the production of heat and in the consumption of oxygen is caused by the growing mass of active protoplasmic tissue (fetal and maternal), and that the maternal production of energy per unit of mass remains unchanged. Rowe and Boyd<sup>29</sup> have recently presented evidence that this is not the case and that, in addition to the factors already mentioned, the excess production of heat is in part dependent on some unknown mechanism engendered by the state of pregnancy. Whatever may be its cause, it is possible that the increase in total metabolism may affect certain factors which enter into the maintenance of the normal elimination of urea, particularly the rate and volume of blood flow through the kidneys.

The concept of the blood urea clearance as a mathematical expression of renal functional activity is based on certain physiologic factors which determine the rate of elimination of urea from the blood under conditions of normal metabolism and blood flow in the nonpregnant state. It seems obvious that alterations in these physiologic factors may occur during pregnancy in view of the profound alterations in protein metabolism and circulation which are associated with that state. Because of the fact that the magnitude of these changes increases progressively throughout the period of gestation, it would appear probable that their effect on the elimination of urea, if they have such an effect, should become more marked in the later months of pregnancy. From our observations of normal pregnant women, we are of the opinion that the end-result of these physiologic changes, particularly the increasing retention of nitrogenous substances, although counteracted to a certain extent by the slightly diminished concentration of urea in the blood, is a diminution in the blood urea clearance values as calculated on the basis of formulas which represent normal conditions in the nonpregnant state. Furthermore, the extreme variability of many of these physiologic changes in different women during pregnancy introduces uncontrollable and variable factors which may render the interpretation of the blood urea clearance findings extremely difficult.

Certain observations made by Goldring<sup>30</sup> may be of significance in this connection. He found that during the acute febrile stage of rheumatic infection the values for blood urea clearance were usually higher than the highest values observed in normal persons, and that

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29. Rowe, A. W., and Boyd, W. C.: *The Metabolism in Pregnancy: Foetal Influence on Basal Rate, Nutrition* 5:551, 1932.

30. Goldring, W.: *Studies on the Kidney in Acute Infection: II. Observations with the Urea Clearance Test in Acute Rheumatic Infection*, *J. Clin. Investigation* 10:345, 1931.

during the afebrile convalescent period the values were usually lower than the lowest observed normal values, returning to normal within about two weeks. These findings were interpreted as indicating a state of renal hyperfunction during the acute stage, as a response to the demand for increased protein catabolism, and a state of renal hypofunction during the convalescent period, probably a result of toxic injury to the renal parenchyma. Whereas this interpretation may be correct, it is also possible that the subnormal values obtained during the period of convalescence may be in some way related to the state of positive nitrogen balance and protein storage which usually follows the prolonged state of negative balance and increased protein catabolism associated with febrile disorders. The condition during convalescence would in this respect be analogous to that which exists during the later months of gestation, that during the acute febrile period being analogous to the first few months of pregnancy and the first few days of the puerperium. Interpreted on this basis, our observations during these periods coincide with those of Goldring,<sup>30</sup> this coincidence suggesting the validity of the concept, particularly in view of the fact that his interpretation of the low clearance values during convalescence was apparently not supported by the presence of either clinical or laboratory evidence of renal disease. It seems unlikely that renal dysfunction dependent on an organic renal lesion occurring as a result of prolonged acute infection would consistently fail to manifest itself by some change in the urinary findings.

On the basis of our observations, we feel that the value of the urea clearance test as an accurate index of renal functional efficiency in pregnancy diminishes as the period of gestation lengthens. Subnormal values obtained during the last two months of pregnancy must be interpreted with extreme caution, particularly in the absence of clinical or laboratory evidence of renal functional insufficiency. Investigation of physiologic alterations in protein metabolism and in the rate and volume of blood flow through the kidneys during this period, as well as of the altered relationship between the area of the maternal body surface and the urea elimination, may throw some light on the factors directly responsible for the observed difference between urea clearance in the pregnant and in the nonpregnant state.

#### SUMMARY

1. Determinations of urea clearance were made in thirty-nine cases of normal pregnancy and in seven cases of chronic glomerulonephritis and one of myocardial failure complicating pregnancy.

2. In the normal group, the urea clearance values ranged from 28 to 184 per cent of the average normal as established by Van Slyke and his associates.

3. The urea clearance, which was normal in the first few months of gestation, diminished as pregnancy progressed, being rather consistently low a few days before the onset of labor. High values were obtained during the early days of the puerperal period.

4. It is suggested that these findings may be dependent on changes in total metabolism and protein metabolism, fetal development and alterations in the rate and volume of blood flow through the kidneys.

5. It is further suggested that the laws governing the elimination of urea in the nonpregnant state, which form the basis of the mathematical calculation of the blood urea clearance, may not apply to the pregnant state because of the physiologic changes mentioned.

6. Subnormal clearance values obtained during the last two months of gestation must be interpreted with extreme caution, particularly in the absence of clinical or laboratory evidence of renal dysfunction.

## Book Reviews

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**The Technique of Using Paper Films for Roentgenograms of the Chest.** By M. W. Barnard, M.D.; J. B. Amberson, Jr., M.D., and M. F. Loew, M.D., *American Review of Tuberculosis* **25**:752 (June) 1932. By M. W. Barnard, M.D., *Quarterly Bulletin, The Milbank Memorial Fund* **10**: (April) 1932. By J. B. Amberson, Jr., M.D.; M. W. Barnard, M.D., and M. F. Loew, M.D., *Transactions of Twenty-Eighth Annual Meeting of the National Tuberculosis Association*, 1932.

A review of the investigative work of Amberson, Barnard and Loew on the comparative value of paper and of celluloid films for roentgenograms of the chest leads one to the following conclusions.

The present financial condition has made economic demands, and necessarily workers using the x-rays have been trying to find a suitable substitute for the rather expensive celluloid x-ray film.

The substitute must be of low cost but still compare favorably with the more expensive accepted celluloid film.

The use of a single coated paper is not new; from time to time manufacturers have sold x-ray paper, but the quality has not been satisfactory except for the examination of small parts. Recently manufacturers have brought out an improved paper, and at present many of the large hospitals and clinics are using this paper, especially for follow-up examinations.

The present paper compares quite favorably with the celluloid film, even in the examination of heavier parts, such as the chest and stomach. The application of the paper in examinations of the chest, according to the authors, has been quite satisfactory. They have recently examined 1,000 cases, using both the paper and the celluloid film. The celluloid film always afforded somewhat better clarity and detail, but for diagnostic purposes the two films were in substantial agreement. The authors give a résumé of their cases with comments.

The small pulmonary findings are more apt to be missed when the paper film is used, but the cheapness of the examination makes future check ups economical.

There are difficulties in manufacturing the paper which lead to slight variations in the photosensitiveness of different batches of paper. (The same variations are often encountered with celluloid films.)

Paper films do not produce as clear roentgenograms as do celluloid films. The difference is not sufficient to impair the value of the paper for practical purposes. The slight diagnostic error is offset by the possibility of examining and reexamining large groups economically. The smaller expense (\$1.25 per celluloid film against \$0.40 per paper film) makes the roentgen examination of large groups of school children possible.

**La constipation: Comment l'éviter? Comment la guérir?** By Victor-Pauchet and H. Gaehlinger. With a Preface by Prof. P. Carnot. Second edition. Paper. Price, 38 francs. Pp. 214, with 8 figures. Paris: Gaston Doin & Cie, 1933.

This book, now in its second edition, is an inclusive summary of the art of treating the constipated patient; it contains a systematic review of possible causes of constipation, with descriptions of treatment by medicine, hydrotherapy, physical therapy and surgical measures. Since the book is apparently not intended to be scientific, one cannot complain of features which would otherwise be objectionable; these include the absence of clinical or experimental proof of important assumptions, the lack of a bibliography and index, the uncritical repetition of such statements as the one that "savages defecate three times a day," and the unneces-

sarily unctuous descriptions of a mineral water as "highly mineralized" and "rich in chlorides." The section on surgical treatment sketches briefly a repertory of ectomies, pexies and plicatures for the technical details of which the reader is referred to another work, and mention is made of methods of intestinal antisepsis and vaccination; the absence of specific facts and case histories leaves this section unconvincing. On other points, however, the book contains concisely worded practical suggestions which may be of help in dealing with difficult cases.

**L'exploration de l'intestin: Diagnostic et traitement des maladies et des syndromes.** By R. Morichau-Beauchant. Paper. Price, 42 francs. Pp. 514, with 1 figure. Paris: Gaston Doin & Cie, 1933.

The purpose of this book is to summarize for students and practicing physicians the diagnosis and treatment of disorders of the intestine, and necessarily includes the differential diagnosis of practically all acute and chronic abdominal conditions. In the first of its four parts it deals with methods of examination; in the second, with diagnosis and treatment of diseases and syndromes; in the third, with acute surgical intestinal conditions, and in the fourth, with acute painful nonintestinal conditions. Occasional lack of specific factual detail gives the book an air of superficiality despite its length, and most students would prefer to see an alphabetical index replace part of the twenty-one page table of contents which is placed at the end of the book. Nevertheless, one feels that the author has done commendable work with so great a mass of material and that he achieves his purpose.

**Diet in Sinus Infections and Colds.** By Egon V. Ullmann. Price, \$2. Pp. 116. New York: The Macmillan Company, 1933.

This book, which is prepared apparently for the layman, judging from the elementary language in which it is written, has to do with the implied importance of diet in the prevention and treatment of sinus infections and colds, predicated at first the dietetic treatment of these conditions on the work that has been done in the past in regard to the lack of resistance to infection in the absence of certain vitamins in the diet. The author, however, uses these known facts to slight extent, and bases his concept of the treatment of sinus infection largely on a so-called diet from which salt has been withdrawn. The reviewer knows of no scientific evidence to show that acidosis is responsible for infection or that increasing the body calcium and decreasing the chloride will affect infections of the nature of colds and sinus disorders. The book falls into the category of fadism, based on a minimum of scientific proof.

**The Vitamins in Health and Disease.** By Barnett Sure. Price, \$2. Pp. 206. Baltimore: Williams & Wilkins Company, 1933.

This book, written in a pleasant and authoritative manner, deals systematically with the vitamins along conventional lines. Although the book is well up to date, it must be admitted that little is added to what is already easily available in monographic form. The lengthy table of the vitamin contents of various foods is useful, and the final chapter on clinical applications will appeal to practicing physicians. For the statement on the jacket that "Vitamin deficiency often spells the difference between . . . catching everything that comes along and enjoying freedom from infection," we trust the author is not responsible.

## PERIODICITY OF CARBOHYDRATE METABOLISM AND RHYTHMIC FUNCTIONING OF THE LIVER

THEIR SIGNIFICANCE IN THE TREATMENT OF DIABETES  
WITH INSULIN

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If a diabetic patient is kept on a constant diet somewhat above his carbohydrate tolerance, with other conditions of life, particularly exercise, also constant, the amount of sugar excreted nevertheless will vary from day to day. If frequent samples of urine are examined, the excretion of sugar will be found to vary somewhat, independently of the meals. Some meals are followed by an immediate glycosuria, while others are followed by a slight increase or none. Closer investigation reveals these variations as expressions of a regular daily periodicity. Often in diabetic patients there is a minimum excretion of sugar around noon, even with a constant diet.

In severe diabetes during starvation, Hatlehol<sup>1</sup> found a continuous decrease in the sugar content during the day and an increase during the night, often with the greatest excretion in the early morning hours.

When first encountered, these phenomena were puzzling and inexplicable. Now light has been thrown on them by Forsgren's<sup>2</sup> discovery of the rhythmic functioning of the liver. Since Claude Bernard, the liver has been regarded as the body's chief storehouse of carbohydrate. Its glycogen content has been thought to express the balance between the supply of, and demand for, carbohydrates in the body. Somewhat contrary to this simple view, Forsgren has recently shown that the liver is no such passive storer of glycogen, but a rhythmically functioning organ, alternately storing glycogen and secreting bile. Through microscopic examination Forsgren found that the substance precipitated by barium in the liver of the rabbit varies considerably in amount at different times of the day. The barium precipitate consists chiefly of bile acids, and its quantity is in inverse proportion to the amount

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1. Hatlehol: *Acta med. Scandinav.* (supp. 8), 1924, p. 1.

2. Forsgren: *Klin. Wchnschr.* 8:1110, 1929; *Acta med. Scandinav.* 73:60, 1930.

of carmine-staining glycogen in the liver cells. In determining the glycogen content in the rabbit's liver by Pflueger's method, Forsgren found that it ranged from 1 to 13 per cent in a normal state of nourishment and from 0.25 to 2.5 per cent in starvation. These variations in the barium precipitate on the one hand and glycogen on the other exhibited a pronounced twenty-four hour periodicity, with a maximum amount of glycogen in the small hours of the night and early morning and a minimum at noon, at which time the bile elements were at their maximum. This periodicity was partly independent of meal times, and Forsgren considered it as the expression of a functional rhythm, with alternating secretory processes of assimilation and dissimulation in the liver. Corresponding variations were found in white mice by Holmgren<sup>3</sup> and Ågren, Jorpes and Wilander.<sup>4</sup>

That the liver in man functions with a daily rhythm is indicated by some earlier investigations. Thus Pfaff and Balch<sup>5</sup> found in a

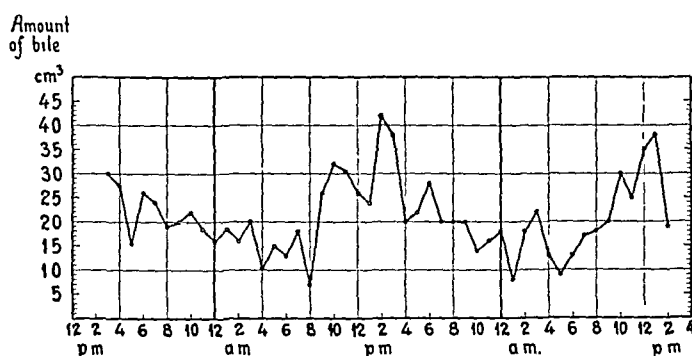


Chart 1.—Curve of bile secretion from Pfaff and Balch (J. Exper. Med. 2:49, 1897).

woman of 38 with a postoperative blind biliary fistula that the maximum secretion of bile occurred periodically and could not be related to the meals. The secretion rose during the day and sank at night. The hourly secretion of bile was capricious and irregular. The greatest amount of bile was excreted at noon, irrespective of the hours for meals. A bile secretion curve of this type, published by Pfaff and Balch, is reproduced in chart 1.

From a comparison of Pfaff's and Balch's observations on secretion of bile, already mentioned, with Forsgren's discovery of the rhythmic functioning of the liver, it appears that in man also there is probably in the liver a maximum secretion of bile occurring simultaneously with a minimum glycogen content and a secretion minimum of bile together with a maximum glycogen content. According to the Pfaff and Balch

3. Holmgren: Ztschr. f. mikr.-anat. Forsch. 24:632, 1931.

4. Ågren, Wilander and Jorpes: Biochem. J. 25:777, 1931.

5. Pfaff and Balch: J. Exper. Med. 2:49, 1897.

curve, one may thus expect a minimum of glycogen at noon and a maximum of glycogen after midnight.

The investigations of Mann and Magath<sup>6</sup> proved that the glycogen of the liver is the material used in the formation of the blood sugar.

Helly<sup>7</sup> found an abundance of glycogen in the livers of diabetic patients, and Paulesco<sup>8</sup> found the same in dogs with pancreatic diabetes after pancreatectomy. Moreover, it has been known since Claude Bernard and Pflueger that the liver can produce glycogen even in starvation. In diabetes, in which regulation of the blood sugar is disturbed, and in starvation, when no alimentary disturbances are manifest, Hatlehol also found a regular daily periodicity, viz., a decrease

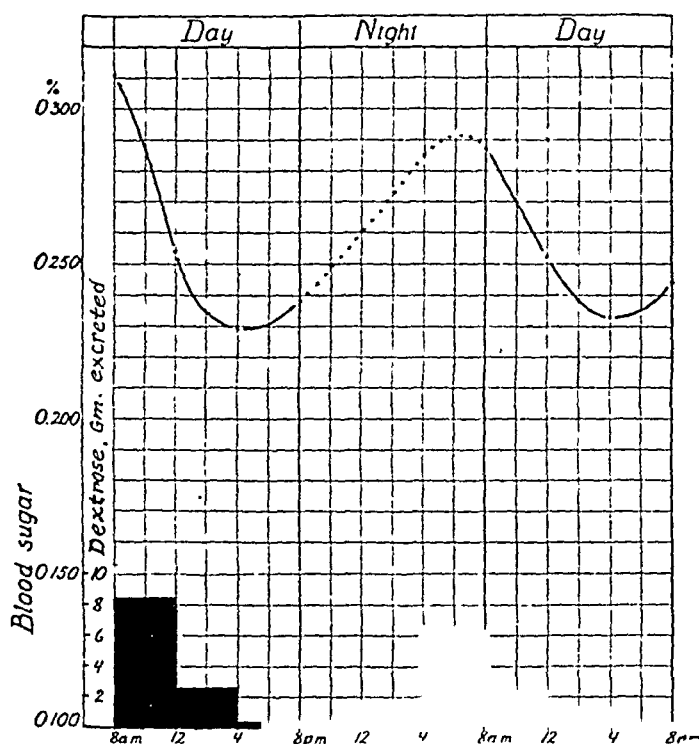


Chart 2.—Blood sugar curve from Hatlehol (*Acta med. Scandinav.* [supp. 8], 1924, p. 1).

of the blood sugar during the day and an increase at night, with a maximum excretion in the early morning hours. Chart 2 is a reproduction of one of Hatlehol's curves.

When food is taken, there is less regularity. The effects of absorbed nourishment, varying conditions of nutrition, excretion of sugar in the urine, etc., may be disturbing factors. However, sporadic observations have been made which suggest that even when nourishment is taken, the rhythm with which the liver functions may be manifest.

6. Mann, F. C., and Magath, T. B.: *Studies on the Physiology of the Liver*, *Arch. Int. Med.* **30**:73 (July) 1922.

7. Helly: *Ztschr. f. exper. Path. u. Therap.* **15**:464, 1914.

8. Paulesco: *Compt. rend. Soc. de biol.* **83**:562, 1920.



K. Petrén<sup>9</sup> was the first to observe that in some diabetic patients the blood sugar curve has occasionally a tendency to sink toward the afternoon, irrespective of meals, and that blood sugar values may then be obtained which are lower than the starvation values of the morning. He also found that some meals are not followed by any increase in blood sugar, but he could give no adequate explanation for this. The rhythmic functioning of the liver gives a natural explanation of the phenomenon. It is only to be expected that the sugar curve will show reduced susceptibility to nourishment if a meal is absorbed during the assimilatory stage of liver function with a deposition of glycogen.

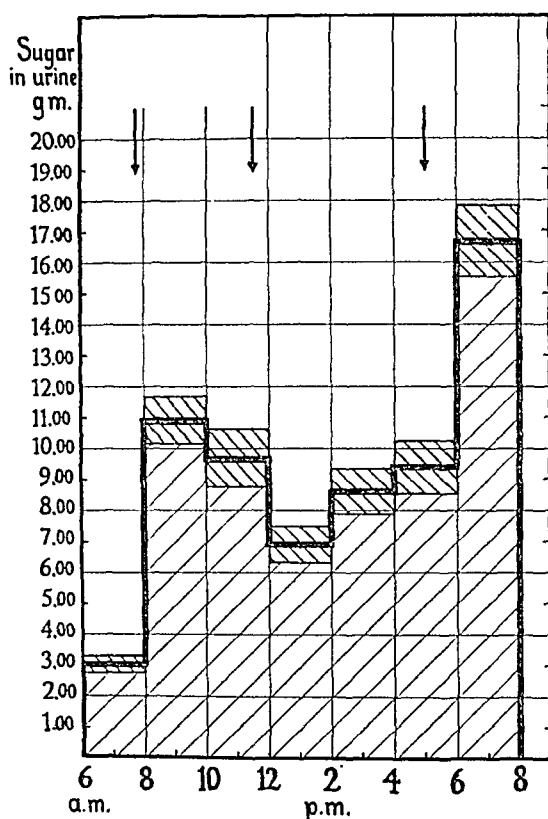


Chart 3 (case 1).—Urinary excretion of sugar.

Table 1 and chart 3 give the two hour sugar excretion of a subject who for twenty-three days was on a diet of 72 Gm. of protein and 160 Gm. of carbohydrate, the three daily meals being given at 7:45 and 11:30 a. m. and 5 p. m.

The time of the meals is indicated in the charts by arrows. The first and third meals were followed by a great and immediate increase in excretion, while after the second meal there was no such increase. This situation is particularly marked in patients kept on diets only slightly exceeding the limits of tolerance.

9. Petrén: *Diabetes Studier*, Copenhagen, Gyldendalske Boghandel, 1923.

In order to throw light on these questions, I made a systematic investigation of the effect of diet on the blood sugar curve. Tests were made on five different days. The food on the test days was always the same and consisted of twelve or twenty-four Albert biscuits,<sup>9a</sup> 96 Gm. of cheese, 96 Gm. of butter and 480 Gm. of milk. In addition, 100 Gm. of water was given every half hour. The composition of the meals was the same on each test day, but their number varied and the intervals between them ranged on the different test days from half an hour to four and a half hours. The capillary blood was tested by

TABLE 1.—*Excretion of Sugar in Case 1*

	Sugar in Urine, Gm. per 2 Hours						
	A. M.			P. M.			
	6-8	8-10	10-12	12-2	2-4	4-6	6-8
1929	a	a	a	a	a	a	a
October 7	1.4	7.8	12.7	5.2	3.2	3.7	17.6
8	3.1	13.9	20.0	5.9	5.1	5.8	13.3
9	2.2	6.4	15.2	6.2	3.8	7.5	12.5
10	2.6	10.6	9.9	6.3	7.1	11.5	13.4
11	2.0	5.0	6.8	6.4	6.3	20.4	15.6
14	4.8	8.9	8.6	6.9	4.4	5.7	7.8
15	2.3	9.0	5.4	5.9	7.2	4.9	33.1
16	3.7	11.7	19.7	11.5	16.4	3.7	7.0
17	2.5	8.8	9.1	3.3	7.4	10.3	19.4
18	2.6	8.1	8.8	4.6	11.8	9.5	13.2
21	5.5	14.5	11.3	10.7	7.9	12.3	21.9
22	3.6	18.1	7.4	7.9	9.0	9.2	25.9
23	4.3	16.0	12.6	8.6	16.2	12.8	17.9
24	3.0	8.0	10.3	6.7	10.8	4.8	10.5
25	2.0	5.9	12.6	5.6	9.9	10.8	16.3
28	3.1	13.7	4.4	6.8	10.8	14.4	21.7
29	2.3	15.4	6.3	1.8	9.8	10.8	22.5
30	0.7	10.0	10.0	7.5	11.5	12.3	23.2
November 5	3.7	10.9	8.6	9.6	11.2	12.4	8.8
8	5.4	12.3	3.0	2.3	9.3	11.2	15.4
13	0.9	10.3	7.8	12.2	6.9	4.2	16.3
14	3.2	8.9	7.8	9.7	7.5	10.5	13.7
15	3.9	17.3	3.7	6.8	3.8	3.4	11.4
$M_{\pm}$ =	$3.0 \pm 0.3$	$10.9 \pm 0.8$	$9.7 \pm 0.9$	$6.9 \pm 0.6$	$8.6 \pm 0.8$	$9.4 \pm 0.9$	$16.7 \pm 1.2$

the Hagedorn method, specimens being taken at least every half hour from 8 a. m. to 8 p. m., with two or more starvation specimens between 7 and 8 a.m. Quantitative sugar and acetone tests were made on the urine, also every half hour.

The standard test series included the following daily tests: (a) twenty-four identical meals every half-hour from 8 a. m. to 7:30 p. m.; (b) eight identical meals, at 8, 9:30 and 11 a. m. and at 12:30, 2, 3:30, 5 and 6:30 p. m.; (c) four identical meals, at 8 and 11 a. m. and at 2 and 5 p. m.; (d) four identical meals, at 8 and 9:30 a. m. and

9a. The Albert biscuit is a standard biscuit used in Sweden, with the following constant composition per hundred grams: protein, 11 Gm.; fat, 4.6 Gm., and carbohydrate, 73.30 Gm., corresponding to 388 calories. Each biscuit has a weight of about 9 Gm.

at 12:30 and 3:30 p. m.; (e) four identical meals, at 8 a. m. and at 12:30, 3:30 and 6:30 p. m.

It then appeared that the blood sugar curves in the different daily tests varied. One meal might be followed by a marked, transient increase in blood sugar; another, by more prolonged hyperglycemia; a third might have comparatively little effect on the curve, etc. When the one and a half hour intervals were fixed at 8, 9:30, 11, etc., and the meals given at these hours immediately after the blood sugar determination (chart 4), irrespective of its shape otherwise, the difference curve for blood sugar values between 8 and 9:30 was an ascending one and between 9:30 and 11 a descending one; between 11 and 12:30 there was none, etc.

The daily periodicity is more distinctly apparent if the results of several test days are added, especially if the meal hours on the different

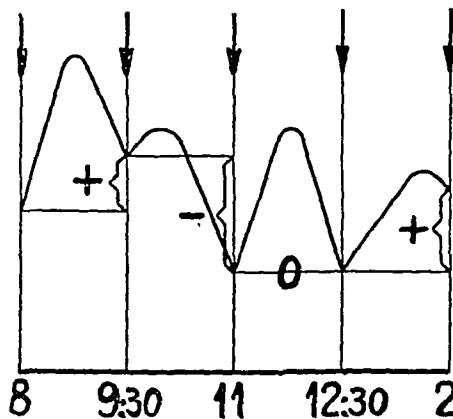


Chart 4.—Chart showing difference curve for values obtained at one and a half hour intervals.

test days are changed so that the more transient effects of alimentary irritation are neutralized.

In this investigation,<sup>10</sup> a total of one hundred and eighty-eight series of daily tests were made. The following is an example of these tests:

CASE 2.—Hanna G., 62 years old, had cardio-arteriosclerosis and glycosuria.

Standard tests of types A, B, C, D and E were made on May 6, June 4, 14 and 21 and August 15. Table 2 and chart 5 give the values obtained for the excretion of sugar in the blood and urine.

The increase in the blood sugar content between 7 and 8 a. m. is noteworthy, since no food was given at that time. There was no external reason for the increase in the starvation value. This phenomenon is the same as that described by Hatlehol.

The difference curve is reproduced graphically in chart 6, which also includes data on the excretion of sugar in the urine and the time of the meals.

10. Möllerström, J.: *Acta Soc. med. suecanae* 56:211, 1930.

TABLE 2.—Results of Standard Tests in Case 2

		May 6, 1929 Test A		June 4, 1929 Test C		June 14, 1929 Test D		June 21, 1929 Test E		Aug. 15, 1929 Test B	
		Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm.
A. M.	7:00	119±7	0	149±2	0	164±1.5	0	154±1.5	0	134±0.5	0
	8:00	159±0	0	173±3.5	0	165±2.5	0	201±3.5	0	169±1.5	0
	8:15	163±10	0	167±2.5	0	—	0	192±1.5	0	180±1.5	0
	8:30	180—	0	186±1.5	0	175±1	0	208±2	0	186±1	0
	8:45	197±0	0	211±1	0	217±2	0	220±0	0	203±0	0
	9:00	197±3	0	227±2	0	224±0.5	0	234±1	0	215±2	0
	9:30	203—	0	229±2	0.23	223±1.5	0	227±0	0.24	222±0	0.07
	10:00	197—	0	220±0	0.20	233±1	0	206±0	0	226±0	0.06
	10:30	194±3	0	215±1	0	239±1	0.25	187±1	0	241±0	0.17
	11:00	190±1.5	0	186±1.5	0	222±1	0.24	166±2.5	0	233±1	0.35
	11:30	182±3.5	0	189±2	0	209±2	0.08	150±0	0	200±0	0.05
P. M.	12:00	205±1.5	0	188±1	0	205±0.5	0	125±4.5	0	206±1	0.08
	12:30	205±7.5	0	193±2	0	174±0	0	120±0	0	210±5	0
	1:00	194±3	0	197±2	0	183±0.5	0	151±1	0	179±0	0
	1:30	196±1.5	0	198±1	0	193±1.5	0	169±1	0	192±0	0
	2:00	188±3	0	178±0	0	194±0	0	180±1	0	194±2	0
	2:30	166±4	0	172±1	0	178±2	0	177±2	0	174±0	0
	3:00	193±9.5	0	176±0	0	171±0	0	167±3	0	200±3.5	0
	3:30	198±1	0.05	180±0	0	163±2.5	0	157±2.5	0	205±0	0
	4:00	192±2	0.05	175±1.5	0	184±3.5	0	173±0.5	0	191±1	0
	4:30	176±1	0.10	172±1	0	182±0	0	206—	0	199±1	0
	5:00	218±3	0.10	170±1	0	187±0	0	204±0	0	205±4	0
	5:30	220±4	0.10	169±0	0	187±2	0	196±1	0	203±2	0
	6:00	206±3	0.8	181±1	0	187±0	0	183±1.5	0	211±2	0
	6:30	239±2.5	0.10	216—	0	193±0	0	159±3	0	197±3	0
	7:00	236±1	0.20	222±2	0	183±1	0	171±0	0	190±1	0
	7:30	230±2	0.17	213±0	0.08	184±1.5	0	187±0	0	203±1	0
	8:00	223±1.5	0.20	193±2.5	0	166±0	0	198±2	0	183±1	0

From the primary observations the results given in table 3 were derived.

TABLE 3.—Additional Data in Case 2

		Blood Sugar Differences, Mg. per 100 Cc.																	
Test	Date	Starv.	8-9:30		9:30-11		11-12:30		12:30-2		2-3:30		3:30-5		5-6:30		6:30-8		
		Value	A. M.		A. M.		A. M.		P. M.		P. M.		P. M.		P. M.		P. M.		
		7-8	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	
A.....	5/ 6/29	40	..	44	..	..	13	15	..	..	17	10	..	20	..	21	..	..	16
C.....	6/ 4/29	24	..	56	..	..	43	7	..	..	15	2	..	..	10	46	..	..	23
D.....	6/14/29	1	..	53	..	..	1	..	48	20	..	..	31	24	..	6	..	..	27
E.....	6/21/29	47	..	26	..	..	61	..	46	60	..	..	23	47	..	..	45	39	..
B.....	8/15/29	35	..	53	..	11	..	..	23	..	16	11	..	0	..	..	8	..	14
		+147																	
		Σ		+237		-107		-25		+32		-31		+81		+20		-41	
		Sugar in Urine, Gm. per 1½ Hours																	
Test	Date	8-9:30	9:30-11	11-12:30	12:30-2	2-3:30	3:30-5	5-6:30	6:30-8										
A.....	5/ 6/29	0	0	0	0	0.05	0.25	0.28	0.57										
C.....	6/ 4/29	0.23	0.20	0	0	0	0	0	0.03										
D.....	6/14/29	0	0.40	0.08	0	0	0	0	0										
E.....	6/21/29	0.24	0	0	0	0	0	0	0										
B.....	8/15/29	0.07	0.58	0.13	0	0	0	0	0										
		Σ 0.54	1.27	0.21	0	0.05	0.25	0.28	0.65										

Σ represents the value for the difference of curve.

In spite of the uniform meals, there was comparatively increased tolerance to nourishment between about 11 a. m. and 3 p. m. This is reflected in the excretion of sugar in the urine. When all the half-hour values are used, the same results are obtained, as chart 6 shows. This chart also includes a planimeter diagram.

For control, two new daily tests, *F* and *G* (chart 5), were made in which the same amount of food as in the other tests was given in a single meal. In test *F*, this meal was taken just before the first maximum of the difference curve, and in test *G*, seven hours later, corresponding to the minimum of the difference curve. In neither case had the subject taken any food since 5 p. m. the previous day. The interesting circumstance then transpired that in the former case the post-alimentary hyperglycemia reached its maximum within one hour after the meal,

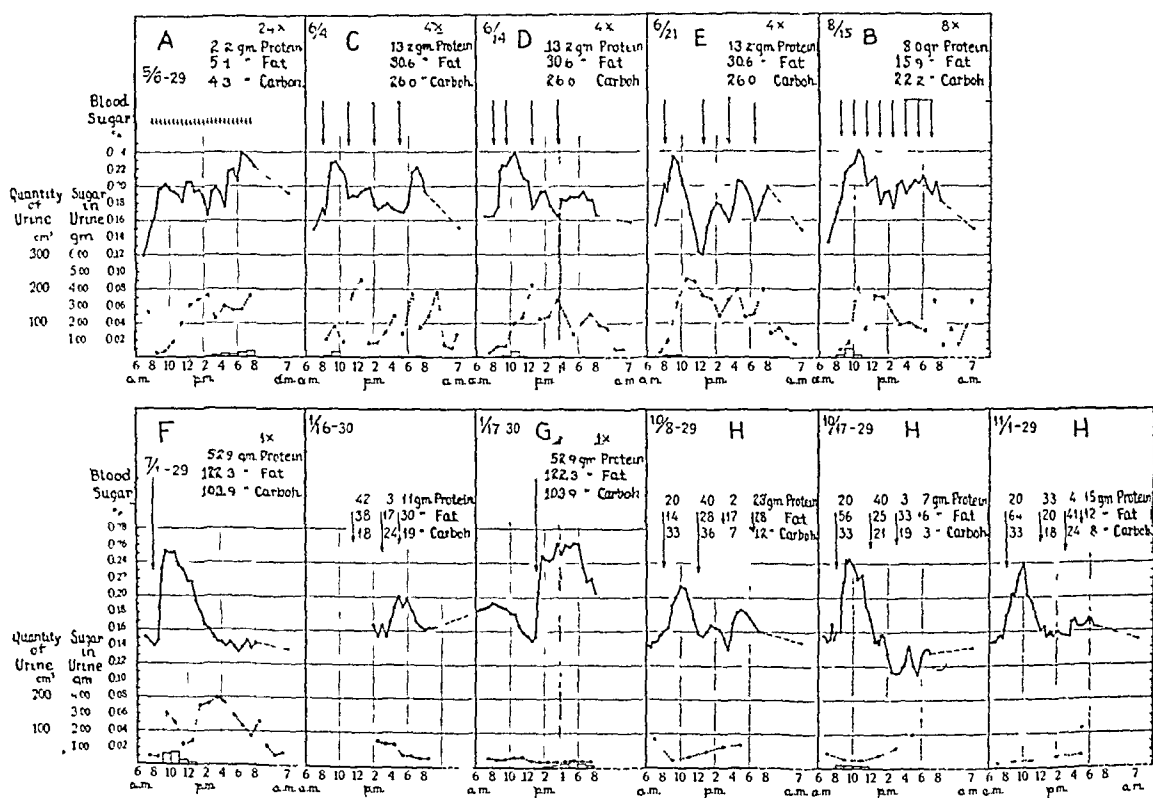


Chart 5 (case 2).—Curves for capillary blood sugar (solid line) and quantity of urine (dotted line). The crossed-barred areas indicate the amount of sugar in the urine.

and seven hours later it had disappeared. In the second case, on the other hand, the post-alimentary hyperglycemia curve was of another type, not reaching its maximum until five hours after the meal, at a time when the difference curve presented its second maximum. The hyperglycemia had not yet disappeared after seven hours.

This dissimilarity in the course of the hyperglycemia curves may be explained by the consideration that digestion and absorption in the two tests took place at different phases of the functional rhythm of the liver. Obviously, a protracted effect is to be expected from the gradual digestion and absorption of so large an amount of food taken at one time.

In accord with the difference between the blood sugar curves, the sugar excretion in the urine also is of another type. Chart 7 shows in greater detail the sugar excretion in the urine at half-hour intervals for the two tests *F* and *G*. In test *F* there is early glycosuria, reaching its maximum after two hours and disappearing after five hours. The total amount of sugar passed with the urine in this case was 1.8 Gm. But if the meal is taken seven hours later, as was the case in test *G*, the glycosuria increases slowly, not reaching its maximum until four hours

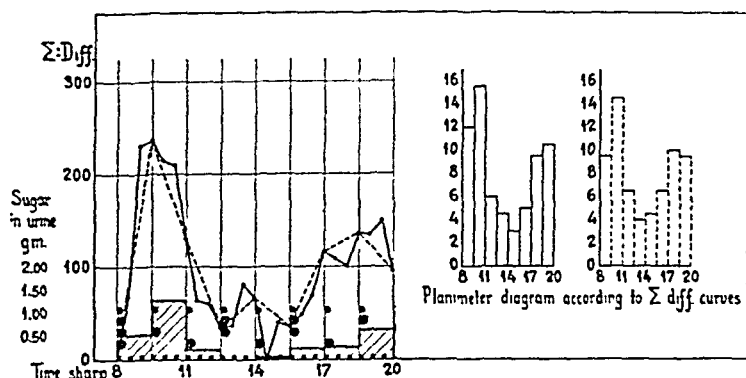


Chart 6 (case 2).—Difference curve with half-hour values (solid line) and hour and a half values (dotted line). The cross-barred areas indicate the amount of sugar in the urine; the black dots, the time of nourishment.

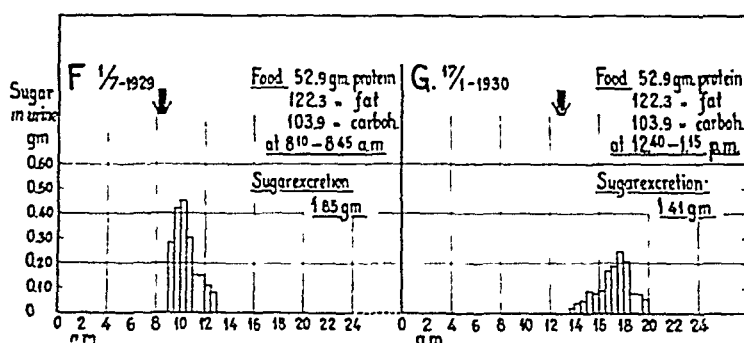


Chart 7 (case 2).—Urinary excretion of sugar.

later, at the time the difference curve for tests *A* to *E* shows its second maximum, and disappearing only after seven hours. The total amount of excreted sugar in this case was only 1.4 Gm. This verifies the supposition that the affinity of the liver for the absorbed nourishment differs at different stages of liver function; in the assimilatory stage with deposition of glycogen, the carbohydrate retention is greater than in the dissimilatory and secretory stage. The greatest affinity may reasonably be expected at the time when the dissimilatory stage changes into the assimilatory one, i. e., when the secretion of bile has passed its maximum. The bile secretion curve of Pfaff and Balch furnishes the key to the interpretation of this phenomenon.

The time of maximum secretion of bile, as shown in chart 1, is the same as that at which one sometimes finds the paradoxical decreases in blood sugar values already demonstrated by Petré, *values which in spite of the intake of food are lower than starvation values*. Charts

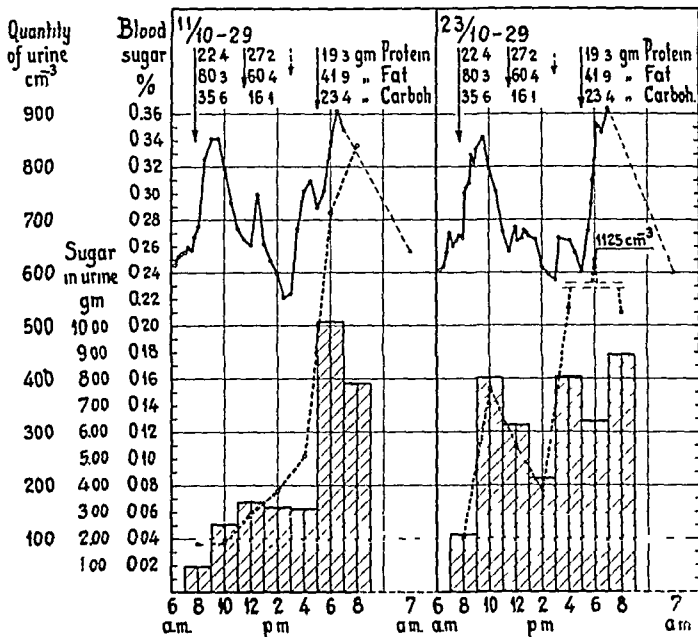


Chart 8 (case 1).—Curves for the capillary blood sugar (solid line) and quantity of urine (dotted line). The cross-barred areas indicate the amount of sugar in the urine.

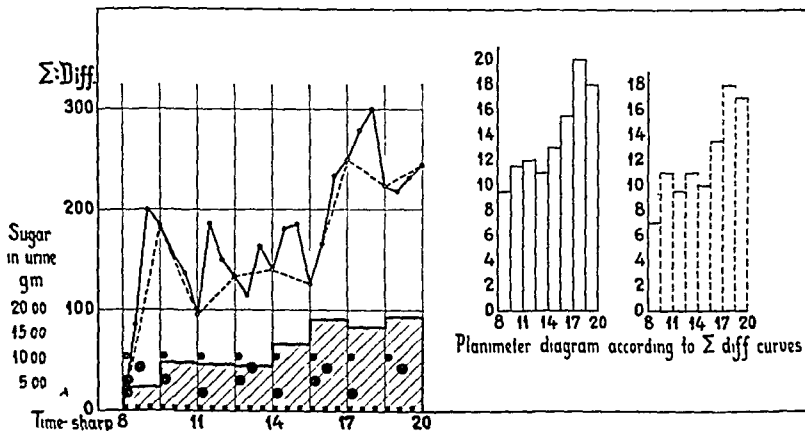


Chart 9 (case 1).—Difference curves with half-hour values (solid line) and hour and a half values (dotted line). The cross-barred areas indicate the amount of sugar in the urine; the black dots, the time of nourishment.

5 E and H and 8 give examples of this. Such a phenomenon cannot possibly be explained by differences in the emptying of the stomach, in digestion or in intestinal absorption, but it can very well be explained by reference to the periodicity of liver function.

The endogenous periodicity apparent in these difference curves varies in different subjects, as charts 9 and 10 show. In some cases the morning maximum of susceptibility to nourishment is greater, and the evening maximum less, while in others the reverse is true. In many cases, the morning and evening maxima are equal, and in these there is at noon a distinct minimum of sugar excreted in the urine. In cases of severe diabetes or an overburdened metabolism with a great excretion of sugar, this minimum susceptibility to nourishment is less pronounced.

The varying susceptibility to nourishment is not strictly bound to any special hour; it varies somewhat on different days, just as the secretion of bile varies (chart 1). The body's reaction to nourishment can also not be expected to remain constant at the same time of day

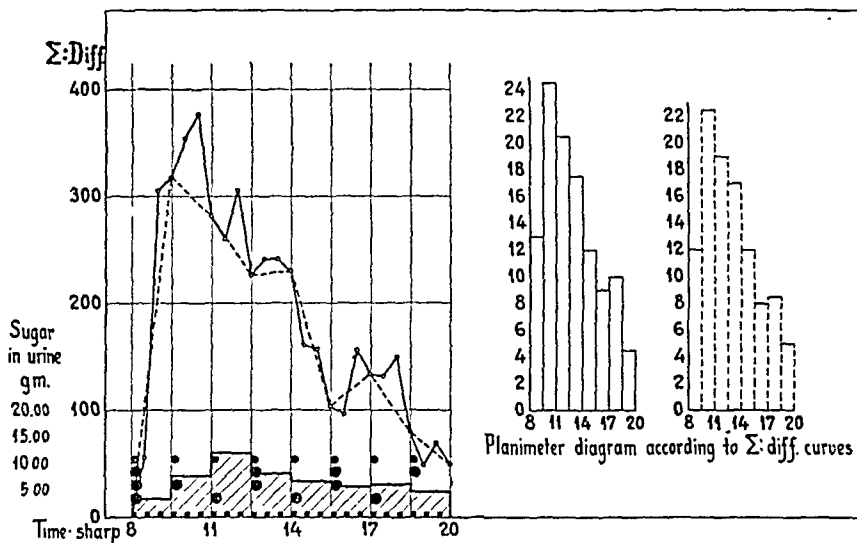


Chart 10 (case 13).—Difference curves with half-hour values (solid line) and hour and a half values (dotted line). The cross-barred areas indicate the amount of sugar in the urine; the black dots, the time of nourishment.

from one day to the next. Chart 11 shows how different the course of the blood sugar curve may be in the same subject under identical test conditions with uniform nourishment and with no change in the state of health.

In disturbances of the blood sugar regulation, when there is overburdening of the metabolism, interference phenomena will appear between the variable endogenous factors and the exogenous alimentary ones. This may cause considerable change in the course of the post-alimentary blood sugar curve, even when the external test conditions are constant. Endogenous factors may even dominate over the exogenous ones, a possibility which is of importance in a proper judgment of the problem of diabetes. Every food tolerance test in the practical and theoretical study of diabetes must therefore be judged



with caution so long as nothing is known of the endogenous periodicity and the capacity of the body to react to nourishment.

In addition to the daily rhythm of the function of the liver, there are, no doubt, periods of shorter and longer duration. Just as the bile secretion in the Pfaff and Balch curve shows minor rhythms in

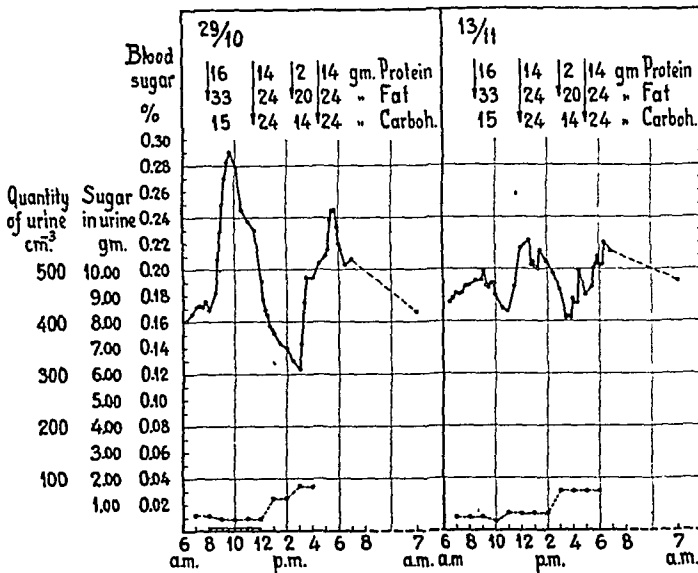


Chart 11 (case 30).—Curves for capillary blood sugar (solid line) and quantity of urine (dotted line). The cross-barred areas indicate the amount of sugar in the urine; the black dots, the time of nourishment.

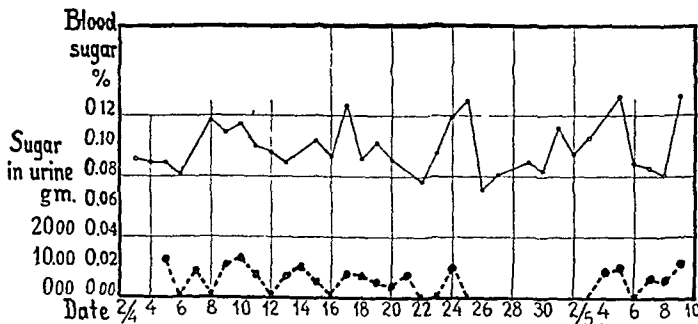


Chart 12 (case 14).—The upper curve indicates the blood sugar (starvation values); the lower curve, the sugar excreted in the urine with the patient on a constant diet.

daily periodicity, corresponding variations must be expected in the assimilatory and dissimilatory functions of the liver. To what this is due is still unknown. In the excretion of sugar of diabetic patients on a constant diet, a regular periodicity can also often be traced, spanning three, four or five days. Chart 12 shows a striking example of a long periodic excretion of sugar in a case of benign glycosuria.

For treatment with insulin, knowledge of the endogenous periodicity of the carbohydrate metabolism is of fundamental importance. Forsgren demonstrated in experiments on animals that susceptibility to insulin varies with the functional stages of the liver and its glycogen content. I found that in patients with severe diabetes treated with insulin in whom insulin shock had previously been observed, the latter regularly appeared at a time of day when, according to the standard tests already described, reduced susceptibility of nourishment could be ascertained.

Another example follows:

A diabetic patient, aged 71, excreted a mean amount of 67.9 Gm. of sugar daily on a diet of 34 Gm. of protein, 51 Gm. of fat and 81 Gm. of carbohydrate. On

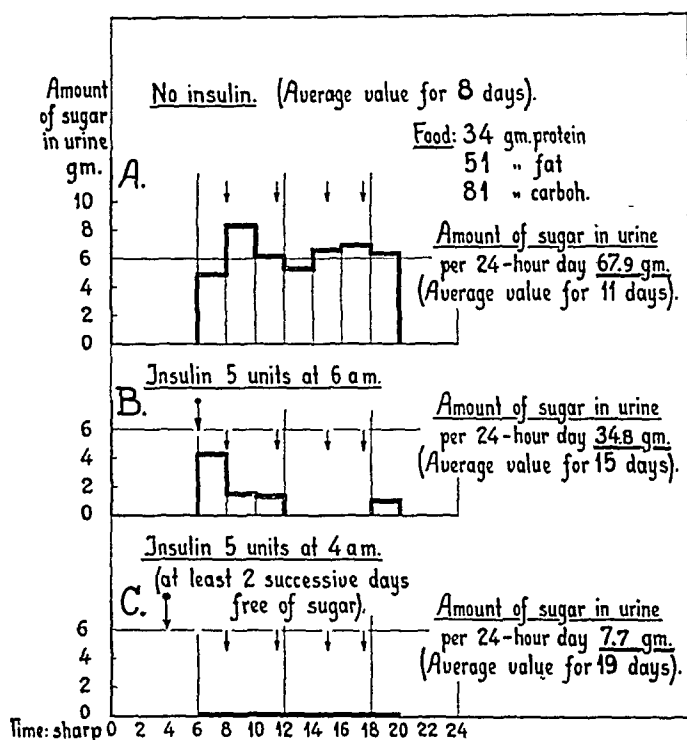


Chart 13.—Urinary excretion of sugar in a patient with diabetes.

this diet, the patient was given 5 units of insulin at 6 a. m., after which the excretion of sugar diminished to a mean of 34.8 Gm. daily. But when the patient on the same diet was given 5 units of insulin at 4 a. m., the excretion of sugar fell to a mean of 7.7 Gm. daily, and, in addition, the urine was quite free from sugar eleven days out of nineteen.

This periodicity of excretion is shown by chart 13 *A*, which gives the mean amount of sugar excreted in the urine at intervals of two hours for eight days. Chart 13 *B* and *C* shows the sugar excretion on the same diet, but with 5 units of insulin given at 6 and 4 a. m., respectively.

This experiment shows that 5 units of insulin will not have the same effect at 6 a. m. as at 4 a. m., its effect at the latter hour being almost twice as great. Since the maximum sugar excretion of this patient took

place between 8 and 10 a. m., the most suitable time for giving insulin in this case was apparently four hours before the maximum excretion of sugar in the urine, irrespective of meals. Ingolf is about to publish a compilation of a large number of cases at the Maria Hospital, Stockholm, in which experience was gained concerning the administration of insulin in the early morning. Independently of my investigations, Tillgren and Ingolf found empirically in many cases that insulin had a more powerful effect when given in the early morning hours. Before the discovery of the endogenous periodicity of the carbohydrate metabolism, this was quite inexplicable. It is the endogenous periodicity of the carbohydrate metabolism, and not the meals, that should determine the dosage of insulin.

Without a doubt many factors cooperate, and the endogenous rhythm is an effect of interference with the cooperating factors, concerning which there is not yet sufficient knowledge. Forsgren's discovery of the rhythmic functioning of the liver indicates the direction in which a profounder study of the internal metabolism should be pursued.

Knowledge of the endogenous periodicity of the carbohydrate metabolism is probably of the greatest moment in the problem of diabetes, as much in diagnosis as in therapy. One may not take it for granted a priori that the reaction of the body is constant from one day to the next, or even from one hour to the next. Of late, the necessity has been emphasized of making daily blood sugar curves if one is to attain a rational insulin therapy. Seyderhelm and Oestreich stated that those cases of diabetes are more benign in which there is a distinct reduction of the noon value of the daily curve. In these, insulin is not considered necessary even when the starvation value of the blood sugar is comparatively high. If, on the other hand, the untreated diabetic patient shows a daily blood sugar curve with an ascending course, his case is regarded by Seyderhelm and Oestreich<sup>11</sup> as a severe one, requiring insulin treatment. The author's tests have a similar implication.

#### SUMMARY

In many cases of diabetes, there is a periodic variation in the effect of nourishment on the blood and urine sugar curves, irrespective of meals. At certain hours of the day, postalimentary hyperglycemia is milder and less prolonged, the sugar excretion in the urine also diminishing. There may be a tendency to spontaneous reduction of the blood sugar content, so that in spite of nourishment, blood sugar values are sometimes obtained which are less than the starvation values. The endogenous periodicity is different in different persons and may change slightly from one day to the next in the same person. This

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11. Seyderhelm and Oestreich: *Ztschr. f. klin. Med.* **109**:35, 1928.

phenomenon is explained by Forsgren's discovery of the rhythmic functioning of the liver, with alternate glycogen production and bile secretion. In the assimilatory stage of the liver function with glycogen production, there is a tendency toward carbohydrate retention in the body, with reduction of the blood sugar content and of the excretion of sugar in the urine; in the dissimilatory or secretory stage the conditions are reversed. The endogenous periodicity of the carbohydrate metabolism is significant for the results of alimentary tolerance tests in diabetic patients, and appears to be of fundamental importance in the development of a rational insulin therapy. Insulin should be administered with due regard for the endogenous rhythm, and not for meal hours.

# EPILEPSY AND CONVULSIONS IN DIABETES

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## INCIDENCE

Extreme rarity of the coexistence of diabetes mellitus and epilepsy apparently has been accepted as a fact. According to Talbot (1930), "Study of the literature has so far failed to reveal a single report of the coincidence of idiopathic epilepsy and true diabetes mellitus." Trumper (1930) maintained that the theoretical incidence of epilepsy in persons with diabetes should be extremely small because of the ketosis and dehydration which are so constantly associated with diabetes and which are so antagonistic to epilepsy. Joslin (1928), writing about epilepsy, stated, "No clear cut case can be found among my 6,000 glycosurias of whom 5,086 are true diabetics." He did, however, mention several possible cases of epilepsy. Subsequent study of Joslin's diabetic patients furnishes the material for the present report.

Bolduan (1932) stated that 2.5 per cent of all deaths in New York City in 1931 were due to diabetes; and Weeks and co-workers (1923) said that "conservative authorities agree that fully 0.4 per cent of the total population" have epilepsy. A study of 19 patients suffering from both diseases is here reported.

Three phases of the subject will be discussed: convulsions dependent on diabetes, convulsions dependent on the diabetic therapy and epilepsy apparently merely coincident with diabetes.

## CONVULSIONS DEPENDENT ON DIABETES

Convulsions as a manifestation of diabetes have been reported many times, particularly in the older literature. Kussmaul (1874) presented the history of a 16 year old diabetic patient with acidosis who was treated with alkali. Two days after treatment convulsions occurred and death ensued. Scheube's (1878) patient with jacksonian epilepsy recovered after the institution of alkaline therapy. Lepine (1888) reported the occurrence of convulsions in a person with severe diabetes. He attributed the symptom to intoxication with formic and oxybutyric acids, since at autopsy no cause was found other than much subarachnoid edema. Lossen (1905) added a case similar to the one reported by Kussmaul. Convulsions and death followed the use of alkali. Stauder's (1906) diabetic patient with convulsions who was relieved by alkali

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From the Joslin Diabetic Unit, New England Deaconess Hospital.

was apparently not acidotic at the time of the seizures. Again, in 1911, Lepine reported a case of diabetic acidosis with convulsions following alkaline therapy. Chauffard and Rendu (1912) reported the case of a young diabetic and alcoholic patient with pulmonary tuberculosis who died following a series of convulsions and in whom at autopsy no renal or cerebral lesion was found. The treatment given was not stated. Labbé, as late as 1920, reported 4 cases of "acidotic epilepsy," in 3 of which alkaline therapy had been used. The treatment in the fourth case was not revealed. One of the patients lived for some time after recovery from the acidosis and suffered no more from convulsions, even in a subsequent and fatal attack of coma.

The experimental work in this field is meager. Gouget (1830) noted the occurrence of convulsions following the injection of acetone bodies into the brains of guinea-pigs. Von Jaksch (1886) produced convulsions in a rabbit placed under a bell jar containing acetone. Dufourt (1911) suggested that asphyxiation might have been the exciting factor, and the suggestion is borne out by the experience of Lennox and Cobb (1928). André and Baylac obtained no such result following the inhalation of acetone. Wilbur (1904) produced convulsions in rabbits by the intravenous administration of *beta*-oxybutyric acid.

Allen and Wishart (1923) studied the effect of the ingestion of various products of fat metabolism in animals. Convulsions were produced in two rabbits. One of these had been given diacetic acid by mouth, but the carbon dioxide-combining power of the blood rose from 38.6 volumes per cent fourteen and a half hours before death to 70 volumes per cent one hour before death. The convulsion occurred at the time of death. The other rabbit had been given butyric acid by mouth. There was a slight convulsion at death when the carbon dioxide-combining power was 33.8 volumes per cent, although this was 50 volumes per cent one and a half hours prior to death. A dog had a convulsion after the intravenous injection of butyric acid, but the carbon dioxide-combining power had been 89.6 volumes per cent only two and a third hours before the seizure and was 61.4 at the time of the convulsion, even after an infusion of saline. Certainly there is little about these experiences that suggests acidosis as the cause of the convulsions, and the authors attributed the convulsion occurring in the dog to alkalosis. Furthermore, Lennox, Nelson and Beetham (1929) found that rabbits fed fat or given injections of lactic acid or acetone were somewhat less susceptible to induced convulsions.

Explanations of this phenomenon have varied. Lepine (1888) attributed the convulsions to intoxication with formic and oxybutyric acids, although in 1909 he seemed to favor individual propensity rather than acetonemia. Dufourt (1911) reviewed the literature on the subject of acidotic epilepsy, and concluded that true diabetic coma is never

accompanied by epileptiform manifestations, and that the convulsions are usually due to uremia or to cerebral lesions or are merely coincidental. Labbé (1920) implied that Dufourt's statement is not entirely warranted, but admitted that it is strange that Naunyn in all his experience never observed convulsions in persons with acidotic diabetes. He concluded his article with the statement that diabetic epilepsy exists, and that it is a manifestation of acidosis and not of hyperglycemia.

Blum (1911) was among the first to assign to alkaline therapy a causative rôle in the production of convulsion in diabetic acidosis, although he admitted the rare existence of acidotic epilepsy. In 1913, in his description of the nervous complications in diabetic coma, he stated that intravenous injections of sodium bicarbonate gave rise to convulsions, whereas the administration of this drug by mouth had had no such effect in the cases he observed. He based his deductions not only on his clinical material but also on the experiments of Stadelmann (1885 and 1889), who produced convulsions in dogs by the injection of soda. However, reference to an article by Stadelmann in 1885 shows that this author used sodium carbonate rather than sodium bicarbonate, and that the symptoms produced in his dogs were so mild that he concluded it was a relatively harmless procedure. Again, in 1889, Stadelmann published the results of intravenous injections of a solution containing both of the aforementioned salts of sodium. Convulsions sometimes occurred in dogs so treated.

In recent years there has been a paucity of reports relating to this subject. Joslin, Root and White (1927) reported 63 cases of severe diabetic acidosis in which alkaline therapy was not used. One of the patients had convulsions, but tetanoid contractions occurred the tenth day after coma, at which time the carbon dioxide-combining power of the plasma was 80 volumes per cent. Thirteen days following coma, she died after a series of convulsions, although the carbon dioxide-combining power of the plasma had dropped to 43 volumes per cent. Autopsy showed marked congestion and edema of the meninges and brain with numerous punctate hemorrhages, in addition to many psammoma bodies and cholesteatomas, but the pathologist stated that no anatomic cause for death was found. Without considering the real cause of the convulsions, it seems fair to say that the ketosis previously present did not produce them.

In 1932, Joslin and his associates reported 179 cases of diabetic coma in which alkaline therapy was not used. Among these is included the case previously described. In addition, another case is described in which convulsions occurred. This case, 9783, was that of a man of 35 years who had had diabetes for three years but had been healthy in every other way. He entered the hospital thirty hours after the onset of symptoms of acidosis. He was drowsy and hyperpneic, but conscious. The carbon dioxide-combining power of the plasma was 4

volumes per cent. The response to treatment during the first six hours was satisfactory, but then the patient became weaker, had convulsions, was cyanotic, and died an hour later after further convulsions and increasing cyanosis. Just prior to death the carbon dioxide-combining power of the plasma was 23 volumes per cent, and the blood sugar, 0.44 per cent. The nonprotein nitrogen on admission was 39 mg. Autopsy was not permitted. Here one sees no definite cause for the convulsions. There was considerable cyanosis, which seemed to follow rather than to precede the convulsions, which appeared to be just a terminal phenomenon. If this case is one of acidotic epilepsy, at any rate it is the only one among 179 cases of diabetic coma. Since the publication of that series of cases, 36 more cases of diabetic coma have been observed in this clinic and in not one of them have there been convulsions.

Of all the published reports of acidotic epilepsy which I have read, none seems conclusive. Often pertinent facts are not given, and in some instances there are causes which seem more likely than the diabetic acidosis. Thus, it seems fair to say that acidotic epilepsy, if it exists, must be rare; and the fact that it was seen formerly when patients were treated with alkali and that it was not observed (with the possible exception of case 9783) in this clinic in a series of 215 patients with diabetic coma treated without alkali implies that Blum (1911) was right in attributing it to the alkaline therapy.

#### CONVULSIONS DEPENDENT ON THE DIABETIC THERAPY

The second phase of the subject of diabetes and epilepsy is closely related to the foregoing one, as may be judged from conclusions reached. One may assume that the alkalosis sometimes occurring after diabetic coma treated with or without alkali may give rise to convulsions in certain persons. It is well known that alkalosis may cause tetany (Collip, 1926, and Lennox and Cobb, 1928). Tileston (1917) stated that sodium bicarbonate administered intravenously caused tetany. Harrop (1919) reported the occurrence of tetany following the intravenous infusion of sodium bicarbonate in a case of anuria due to mercuric poisoning. I have already mentioned Stadelmann's experiments (1885 and 1889) in producing convulsions by the injection of alkali and also Blum's observations (1911 and 1913). Claude and Raffin (1928) found slight alkalinity preceding epileptic seizures. Lennox and Cobb (1928) described cases in which there were increased epileptic attacks following a sudden swing from acidosis to alkalosis, although one patient had no increase in seizures following the slight alkalosis produced by feeding large amounts of alkali. Hence they concluded that "any sudden upsetting of the acid-base balance toward the alkaline side" may give rise to an increased number of epileptic attacks. This may well account for the convulsions formerly observed in diabetic



acidosis treated with alkali and is added reason for caution in the use of alkali in such cases, as has been pointed out by Joslin (1928).

But a more important phase of the subject nowadays is the use of insulin in the treatment of diabetes. The relationship between hypoglycemia and convulsive seizures is gradually attaining greater prominence in the literature. Behrendt and Hopmann (1924) and Waltner (1925) demonstrated that hypoglycemia is associated with an increased irritability of muscle or nerve tissue to galvanic stimuli. Wladyczko (1925) stated that there are epileptic persons whose attacks are provoked by hypoglycemia. Howland and co-workers (1929) and Carr and co-workers (1931) reported convulsions brought about by hypoglycemia resulting from a tumor of the pancreas. Removal of the tumor resulted in a cure. Convulsions due to injected insulin have often been reported (Joslin, 1928, and Woodyatt, 1922).

Any patient treated with insulin must be watched for hypoglycemic reactions, no matter how small the dose of insulin or how infrequently it is given. In case 8990 there was a mild hypoglycemic reaction fifteen and three-quarter hours after an injection of 6 units of insulin in spite of three intervening meals. Occasionally convulsive seizures represent a manifestation merely of hypoglycemia. Sometimes the cause of the convulsion is obviously hypoglycemia, either spontaneous, as in the case reported by Carr and co-workers (1931), or induced by injected insulin; but at times it is difficult to prove that hypoglycemia is the cause and the only cause. A few of our epileptic patients were at first thought to have had convulsions only as a result of hypoglycemia, but they had subsequent attacks without hypoglycemia, and this coupled with the later course of the condition indicated that they had true epilepsy.

The mechanism of the production of these convulsions is not well understood. Probably it could best be included under the explosive theory, as explained by Lennox and Cobb (1928, p. 129). Olmstead and Taylor (1924) found evidence suggesting that deficiency of oxygen might be related to the convulsions. MacLeod (1926) gave a good discussion of the mechanism of both the therapeutic and the toxic action of insulin. In 1928, he maintained that the upset in the neuromuscular mechanism must be caused, not so much by hypoglycemia per se, as "by some agent the development of which is normally prevented by the presence of a certain percentage of glucose." Furthermore, this convulsive phenomenon must occur through the intermediary action of the nervous system rather than by local change in the muscles, since section of the nerve supply to a group of muscles will prevent convulsions of these muscles even when convulsions occur in other groups of muscles.

Why some persons with hypoglycemia have convulsions and others do not is unknown. Possibly there is some epileptic tendency in the

former, which excessive stress may make manifest. It is interesting to note that 5 (cases 3019, 7089, 8042, 8217 and 10270) and possibly 6 (case 5562) of our epileptic patients were at first thought to have had convulsions due merely to a reaction from insulin. Twenty-five patients (cases 2476, 2528, 2633, 2979, 3778, 4022, 4242, 4650, 4715, 5181, 5615, 5830, 7145, 7191, 7592, 8213, 8217, 8316, 8657, 9077, 9382, 9736, 9782, 10442 and 11140) with convulsions apparently hypoglycemic have so far shown no other evidence of epilepsy. The patient in case 5615 had positive bilateral Babinski reflexes, but no cerebral lesion was found at autopsy; Anderson (1931) called attention to this finding in hypoglycemia and to its absence in diabetic coma. Subsequent observation of these cases will be of interest. The aforementioned 6 patients were children, and children are more subject to epilepsy and to hypoglycemic convulsions brought about by injections of insulin than are adults. It is generally conceded that anginal attacks (Hétenyi, 1927, and Root and Graybiel, 1931) or even coronary thrombosis (Blotner, 1930, and Parsonnet and Hyman, 1931) may be induced by an overdose of insulin, and Wohlwill (1928) reported cerebral lesions attributed to hypoglycemia. Drabkin and Shilkret (1927) noted intravascular clotting of blood in a dehydrated dog following the injection of insulin. Lawrence and Hollins (1928) reported 2 cases of hematuria attributed to insulin therapy. Combine these statements with Olkon's (1930) belief that "genuine epilepsy" is dependent on capillary hemorrhages occurring at birth, and one finds that there is some evidence favoring the supposition that hypoglycemia may occasionally be the cause of cerebral lesions which may give rise to epilepsy. Nevertheless, most of these clinical observations involved patients with a known potentiality for such vascular damage. However, the patient in case 3729, a young woman with no obvious arteriosclerosis, suffered for several days from what was believed to be monoplegia due to insulin, which began abruptly with unconsciousness and frothing at the mouth. Again, Joslin (1928) reported paralysis of a few days' duration caused by hypoglycemia thought to be due to insulin in a boy (case 2856) of 14 years.

In our cases of convulsions due to insulin we have noted no dehydration that might, according to Andrews and Schlegel (1927), have exaggerated the effect of insulin. Nor have we ever seen hypoglycemia cause convulsions in persons with diabetic coma, the condition causing the greatest dehydration in diabetic patients; and this is compatible with the assertion of Drabkin and Shilkret (1927) that the dose of insulin sufficient to cause hypoglycemic convulsions in normal animals caused no convulsions in dehydrated animals. Hypoglycemia seldom manifests itself clinically in cases of diabetic coma with or without unconsciousness. The absence of convulsions in persons with diabetic coma in whom hypoglycemia has been induced by treatment with insulin pos-

sibly may be explained partly by the presence of large amounts of fat and acetone (Lennox, Nelson and Beetham, 1929).

Convulsions in a diabetic patient should always be the signal for a determination of the blood sugar, since convulsions in diabetic patients are often due solely to hypoglycemia and are relieved promptly by the administration of an adequate amount of dextrose or other proper carbohydrate. The mere coincidence of convulsions and hypoglycemia should not preclude the diagnosis of epilepsy. Further observation and determinations of blood sugar during the seizures are necessary.

#### EPILEPSY APPARENTLY MERELY COINCIDENT WITH DIABETES

In the literature there is little concerning the coincidence of diabetes and idiopathic epilepsy except references to its rarity. The difference in the age incidence of diabetes and epilepsy discloses at least one reason for this rarity. Joslin (1928) stated that 66.6 per cent of his patients with diabetes had the onset of their disease after the age of 40 years, whereas Talbot (1930) compiled a table which shows that only 2.7 per cent of epileptic persons acquire epilepsy after the age of 40 years. The foregoing facts show the fallacy of Trumper's (1930) argument that "theoretically the incidence of epilepsy in diabetics should be extremely rare since ketosis and dehydration which are prominent features of diabetes constitute a mechanism which is in direct antagonism to the underlying features of epilepsy." The manifestations of epilepsy would have become apparent before the onset of diabetes in most persons suffering from the latter disease. Furthermore, control of the diabetes usually abolishes both ketosis and dehydration, especially during the present period when diabetic patients are given a fairly liberal allowance of carbohydrates.

Cases of diabetes associated with epilepsy have been reported. Lennox, O'Connor and Bellinger (1927) reported a case of epilepsy occurring with severe diabetes; and Allan (1932) reported 2 instances of epilepsy in a series of 840 diabetic persons. Joslin (1928) mentioned 2 of Dr. Geyelin's cases, and Talbot (1930) cited 2 cases seen by Lennox. Riesman and Fitz-Hugh (1927) reported 3 cases of diabetes associated with convulsions, and Labbé (1920) implied that there are diabetic persons with epilepsy.

Determinations of the blood sugar of epileptic subjects have been made often.<sup>1</sup> Usually the authors state that the values were normal,

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1. See Lennox and Cobb (1928); Weston (1916); Heidema (1919); Schwab (1922); Kooy (1919); Olmsted and Gay (1922); Weeks and co-workers (1923); Holmström (1924); Nielson (1925); Drury and Farren-Ridge (1925); Lennox, O'Connor and Bellinger (1927); Lennox and Bellinger (1927); Osnato and co-workers (1927); Munch-Petersen (1928); Felsen (1930); MacKay and Barbash (1930).

but there is no widely accepted standard for normal. Joslin (1928) accepted as normal a blood sugar level below 0.14 per cent during fasting or below 0.17 per cent at any other time. According to this rigorous standard, there are among the epileptic persons for whom blood sugar determinations have been made many who might be classified as having diabetes. The series of 140 epileptic persons reported by Lennox and Bellinger (1927) contains 49 in whom at least one blood sugar determination was above 164 mg., although 21 of the 49 showed no glycosuria.

Among 9,503 patients with true diabetes seen by Dr. Joslin, there are now 19 with almost undoubted epilepsy, 6 of whom have subnormal mentality, and 3 who are classified tentatively as having epilepsy.<sup>2</sup> If one considers all 22 persons as having epilepsy the incidence of epilepsy among our diabetic patients is 2.3 per thousand. Using tables 25 and 50 (Joslin, 1928) and table 2 (Talbot, 1930) and an accepted incidence of epilepsy of 0.4 per cent among the general population (Weeks and co-workers, 1923) one computes a theoretical incidence of about 1.7 cases of epilepsy among 1,000 diabetic persons of all ages. If the figures of Partridge (1928) are used, the incidence is slightly less. Similarly, the incidence of epilepsy among diabetic persons with the onset of their disease before the age of 15 years is found to be 8.4 per thousand. Actually, we have 9 cases of epilepsy among 839 diabetic patients with the onset of the diabetes before the age of 15 years, thus giving an incidence of 10.7 per thousand among the children. This includes case 5562, which White (1932) attributed to hypoglycemia from insulin; but additional data and further consideration of the case persuade me that the attacks were probably epileptic and not hypoglycemic. However, the child was subject to reactions from insulin and the first epileptic attack may have been due to a hypoglycemia that gave rise to cerebral damage and thus caused the epilepsy, although there is no positive evidence that such damage occurs.

The differential diagnosis of epilepsy in the diabetic person is not always easy. A patient treated with insulin may be having a convulsion due merely to hypoglycemia. A diabetic patient with arteriosclerosis may be suffering from cerebral vascular lesions. Subsequent observation of the case is essential. If insulin has been injected, it is necessary

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2. There is among our diabetic patients one (case 11252) with epilepsy which is attributed to a tumor of the brain by reason of headache, vomiting and papilledema. She has just been transferred to the neurosurgical service at the Boston City Hospital. This case is not included in the present series. Nor are two other cases, case 5367, which is one of definite epilepsy with glycosuria but without proved diabetes, and case 2364. The latter is that of a young man of 22 years, who had been subject to nocturnal convulsions, presumably of hypoglycemic origin; on one occasion he had a convulsion at 5:45 a. m., eleven and three-quarter hours after his previous dose of insulin, a time at which he usually excreted much sugar.

to have the blood sugar determined during each attack and preferably at its onset because, as Kersten (1921) and Rowntree (1926) have stated, the convulsion may give rise to an increase in the blood sugar.

In the cases occurring in children confusion in the diagnosis has occurred chiefly in differentiating between hypoglycemic convulsions and epilepsy. In elderly persons with diabetes one should distinguish between attacks of cerebral vascular disease, hypoglycemic convulsions and epilepsy. Careful and prolonged study of the patient usually clarifies the diagnosis. At any rate, it seems wise in such patients to change the dosage of insulin so that hypoglycemia does not occur, even though slight glycosuria results, and this is usually easily managed. After correction of the dosage of insulin, recurrent attacks of convulsions without subsequent aphasia, mental derangement or muscular paresis and without other obvious cause may well be classified as epilepsy.

The cases about to be presented here have been classified by Joslin first as cases of diabetes and second as cases of epileptic attacks without obvious cause. It is true the patients in cases 1745, 4273 and 5336 were arteriosclerotic, and their seizures, though of the usual epileptic type of both grand and petit mal, may have been dependent on vascular damage in the brain. Case 1745 is interesting in that the local doctor had observed rigidity of the left arm in the attacks, but following a shock which caused paralysis of the left side, no further seizures of any type occurred, even after recovery from the shock. Three years later, diabetes developed. Five years after the first shock the patient had a second on the same side and yet survived this for six years.

Three cases (5313, 7417 and 5562) are classified as doubtful cases of epilepsy: The patient in case 5313 for years had had attacks of stupor, clonic and tonic contractions, and nausea and vomiting. A member of the staff of the Boston Psychopathic Hospital saw her and was unable to say definitely whether the attacks were due to epilepsy or to hysteria. Subsequent to thyroidectomy no attacks occurred for two and a half years, but since then they have reappeared. The patient in case 7417, a woman, aged 38, had had sudden attacks of fainting without any recognizable cause. During one attack she had a convulsion. She had moderately severe diabetes and was taking insulin, but there was no definite evidence either for or against hypoglycemia from the insulin as a cause of the attacks. She had one brother who was a deaf-mute. The third doubtful case of epilepsy has been described. In the other cases there was no reason to doubt the diagnosis of epilepsy.

Diabetes developed in the patient in case 3019 in the nineteenth month of life. At the age of 28 months he began having convulsions, which were at first thought to be due to hypoglycemia. At the age of 3½ years he had an exanthematous infection, presumably measles.

with encephalitis as a sequel. At any rate, after this infection the seizures increased in frequency, and subsequently extreme mental deterioration occurred. Diabetes developed in the patient in case 8042 at the age of 2 years. At 3 years and 8 months, she was brought to the Children's Hospital unconscious and in convulsions. Previously well save for the diabetes, she had awakened laughing in the night and then had had a convulsion. Thereupon the mother gave her 8 units of insulin, although the usual daily dose of 5-0-5 units had been given the previous day. Another convulsion occurred after this. Twelve hours later at the hospital the blood sugar was 0.15 per cent, and the urine was free from sugar. Examination showed definite signs of meningeal disease or disease of the upper motor neurons. Slight intermittent fever followed for seven weeks, with temporary blindness which was attributed by the ophthalmologist to hypoglycemia, and by the pediatricians, to a possible toxic encephalitis. Subsequent to recovery from the infection, the patient had many epileptic attacks and underwent mental deterioration before her death in diabetic coma at the age of 5 years.

As for the diagnosis of the diabetes, there are 2 cases on which doubt might be cast. In case 7999, that of a girl of 13 years without evidence of nephritis, hypertension or any other disease except epilepsy and obesity, there was a trace of glycosuria and the blood sugar was 0.19 per cent. On an unrestricted diet, the patient subsequently had no glycosuria or elevation of the blood sugar. In case 5730, that of a boy of 17 years, there was a trace of glycosuria and the blood sugar was 0.18 per cent. Again there was no disease present except epilepsy. The other patients had definite diabetes, and in 9 the condition was severe. Nineteen of the 22 patients were at one time taking insulin.

In 8 cases the diabetes antedated the epilepsy. The reverse was true in 12 cases, and in 2 cases the onsets of the two diseases were simultaneous. In only 2 cases did the epilepsy cease before the onset of the diabetes, three years before in case 1745, and one year before in case 10353. In no case was it apparent that the diabetes or its treatment gave any relief from the epilepsy. Block (1928-1929) noted that epilepsy ceases after the development of tabes dorsalis. An analogous neurologic condition is rarely caused by diabetes, but so far we have observed the occurrence of it in none of our diabetic patients with epilepsy. Occasionally hypoglycemia from insulin seemed to give rise to a greater number of epileptic seizures as in cases 3019, 5562 and 7089.

The age at the onset of each disease in each patient is given in the accompanying table. In 9 cases the diabetes began before the age of 15 years, and in 7 cases, after the forty-fifth year of life. In 10 cases the epilepsy began before the age of 15 years, and in only 4 cases, after the forty-fifth year.

Concerning the etiology of the epilepsy in these cases, I have listed the doubtful cases and the alternative diagnoses. Two of the children had had intestinal parasites, and 3 of them had infected tonsils. Two patients (cases 5513 and 8514) had thyroid disease; in the former instance the disease was nontoxic and in the latter, toxic. One patient (case 5730) had a skull of the oxycephalic type, and there was some question of hypopituitarism in another patient (case 8622). Vascular disease was present in cases 1745, 4273, 5313, 5336 and 7196. There was a history of injury to the head at the onset of the epilepsy in cases 10645 and 11009. In contrast with the implications in papers by Rome (1911), Spielmeyer (1930), Olkon (1930) and Fincher and Dowman (1931), in most of the cases no definite evidence of organic disease of the brain was found. Neither was heredity apparently important, although careful histories for an epileptic heredity were not taken. The patient in case 6313 had one sister with a tumor of the brain. The patient in case 7417 had a brother who was a deaf-mute. There was a family history of defective mentality, feeble-mindedness or epilepsy in cases 5730, 7089 and 10783. Incidentally, diabetic heredity was present in 9 cases, in none of which there was a family history of mental derangement or epilepsy.

The epilepsy in 3 cases has shown some relationship to the menses. The patient in case 7196 had grand mal prior to the menopause, but only petit mal since. In case 11009 the patient had more than twice as many seizures before the menopause as she had subsequently. Pregnancy increased the number of her seizures but only until parturition. The epilepsy in case 10353 began at puberty and ceased seven years before the menopause. The attacks always came just a few days before the menses, although remissions of six months' duration occasionally occurred. Lennox and Cobb (1928) referred to the "well-known fact that many female patients frequently have seizures near the time of menstrual periods," and they listed the appropriate references. They explained this relationship on the basis of "the increased nervous irritability which many women exhibit at that time." Partridge (1928) and Healey (1928) implied belief in such a relationship. Souques (1931) divided such cases into two types: in the first, epilepsy is associated with normal menses, pregnancy and the period following the menopause, and in the second the seizures occur with abnormal menstruation and disappear with the establishment of normal menses. Okey and Robb's (1925) finding of a decreased tolerance to sugar just before and just after the menses and an absence of any consistent cyclic variation in the blood sugar level during fasting in women tends to exclude hypoglycemia as a cause for frequent epileptic seizures at such times. Okey and Robb did find, however, that the ingestion of dex-

trose led to greater secondary hypoglycemia during menstruation than at any other time.

In the table are listed various observations which may be of interest in comparison with similar data on epileptic persons without diabetes.

Nielson (1925) found an average basal metabolic rate of minus 10 per cent in 18 epileptic persons. Lennox and Wright (1928), in a study of 130 such patients, obtained an average value of minus 3 per cent. Lennox and Cobb (1928) stated that the majority of adults with convulsions have either a normal or a reduced rate of oxygen consumption. Joslin (1928) pointed out that the metabolism in diabetes varies not so much from intrinsic as from extrinsic causes of which the diet is the chief one, and he stated that the metabolism in diabetes varies but little from normal. White (1932), in a study of 86 diabetic children and 17 adolescents with diabetes, found the average basal metabolic rate to be plus 11 per cent (in girls, but plus 12 per cent in boys) and minus 2 per cent, respectively. In 9 of our diabetic patients with epilepsy the average metabolism was plus 4 per cent.

In spite of much study of the blood cholesterol, little definite knowledge has been acquired. Pezzali (1923) found a decrease in the blood cholesterol during epileptic fits, but a subsequent rise. Osnato and co-workers (1927) obtained an average blood cholesterol by the method of Myers and Wardell (normal, from 140 to 160 mg.) of 140 mg. in 22 epileptic patients on a diet consisting of 150 Gm. of carbohydrates, 120 Gm. of protein, and 150 Gm. of fat. They found no correlation between the seizures and the level of the cholesterol. Robinson, Brain and Kay (1927) observed a lower average level of cholesterol in epileptic patients than in normal persons, and a low or falling level of cholesterol prior to the seizures. Goodall (1929) also noted that the blood cholesterol was lower preceding the seizures than in the period between attacks. Gosden, Fox and Brain (1929) obtained low values for epileptic persons, especially within twenty-four hours of a seizure. Their lowest values were obtained in status epilepticus or serial epilepsy. This is in contrast to the emotional hypercholesteremia observed by Lyons (1931). These two papers thereby give evidence that the epileptic convulsions may not be associated with hyperactivity of the sympathetic nervous system to which Tracy (1926) attributed them, since in sympathectomized animals Lyons obtained no hypercholesteremia. The publications of Bloor (1931) and Rabinowitch (1931) make it obvious that a proper interpretation of cholesterol values cannot be made unless the diets of the subjects are taken into consideration. In agreement with this is Barborka's (1930) finding that the level of the cholesterol in his epileptic patients was low, and that a ketogenic diet caused an elevation of cholesterol. In the cases herein described, the cholesterol values are influenced not only by the diet but also by the diabetes or condition



*Cocurrent Diabetes and Epilepsy in Twenty-Two Cases*

Case	Age of Patient at Onset of Epilepsy	Age at Onset of Diabetes	Severity of Diabetes		Weight in per Cent of Normal*	Basal Plasma Metabolite Rate	Chlorides, Mg.	Calcium, Mg.	Phosphorus, Mg.	Cholesterol, Mg.	Diet After Onset of Epilepsy			Later Diet			Effect of Change in Diet
			Mild	Mod-erate							Carbo-hydrate, Gm.	Protein, Gm.	Fat, Gm.	Carbo-hydrate, Gm.	Protein, Gm.	Fat, Gm.	
1745	53.0	65.0	+	..	+17	..	663	...	...	...	No restriction	...	...	...	Peterman diet	78	..
3019	2.3	1.6	..	..	-17	-6 to +9	..	...	4.4	203	...	..	...	16	15	78	..
4273	57.0	59.0	..	+	+25	..	49	...	...	...	88	57	128	131	65	89	No apparent effect
5313	38.0	38.0	..	+	+5	-1 to +2	..	...	...	...	78	60	117	100	66	94	No apparent effect
5336	62.0	67.0	+	..	-11	..	52	...	...	...	133 (?)	41	54	...	..	..	Later carbohy- drate and no at- tacks for 23 days
5562	9.5	4.8	..	..	...	+5 to +17	52	10.4	...	...	84	57	93	45 to 96	..	..	No apparent effect
5730	16.0	17.0	Very mild	..	-10	+20 to +51	..	...	...	...	...	...	...	...	..	..	No apparent effect
7059	10.0	2.0	..	..	+8½	..	..	...	...	...	32 to 85	50 to 60	80 to 100	...	..	..	No apparent effect
7196	24.0	53.0	+	to +	+12	..	..	...	...	...	61	54	42	80 to 147	48	73	No apparent effect
7417	38.0	36.0	..	+	+2	..	50	...	...	...	110	77	135	124	64	93	No apparent effect
7099	10.0	13.0	+	..	...	-7	..	...	...	...	...	..	...	...	..	..	Also has pheno- barbital; fewer attacks
8042	3.7	2.0	..	+	...	..	..	...	...	185	...	..	...	...	..	..	
8217	8.0	4.5	..	..	-3½	..	..	...	...	263	84	47	84	116	73	92	
8514	26.0	38.0	+	to +	+32	+65 to +18	..	...	...	...	120	68	120	122	67	119	
8622	Prior to diabetes mellitus	12.0	..	..	N	-9	..	...	...	108	75	51	86	102	62	115	
9010	37.0	59.0	..	+	-24	..	..	...	...	...	40	60	100	115	53	87	
10270	11.0	6.0	..	..	-12	+8	49	9.0	2.1-3.9	120-206	129	78	104	180	86	84	
10353	13.0	39.0	..	+	-20	..	..	...	5.1	...	Unrestricted	...	...	153	76	81	No apparent effect
10645	5.0	11.0	..	..	-10	..	47-54	11.3	...	216-182	Unrestricted	82	133	...	..	..	
10783	45.0	45.0	+	..	+18	-6	50	...	...	242	158	...	...	...	..	..	
10785	22.0 (?)	23.0	..	+	-19	..	..	...	...	...	Unrestricted	...	...	134	69	93	No apparent effect
11009	15.0	57.0	..	+	N	-5	52	11.7	3.6	298	Low carbohydrate	to high carbohydrate	...	...	...	...	No apparent effect

\* The weight is that at the onset of epilepsy, if known; otherwise the weight is that when the patient was first seen by us.

associated with it. Nevertheless it seems worth while to include them. The average value for the 8 cases studied is 207 mg. (normal, from 180 to 230 mg.).

Spinal puncture was done in 7 of our cases of epileptic diabetes. No evidence of a pathologic process was found, although the total protein was 19 mg. and 15 mg. in 2 of the cases. In 2 cases simultaneous venipuncture was done. In 1 the blood sugar was 0.32 per cent when the spinal fluid sugar was too low to be measured. At the time, the patient was under the influence of ethylene anesthesia. In the other case the blood sugar was 0.26 per cent when the spinal fluid sugar was 0.11 per cent. The ratio of spinal fluid sugar to blood sugar in these cases is considerably lower than that reported by Lennox and Allen (1930) and that by Wahl (1931). Patterson (1929) found spinal fluid sugar low in epileptic persons, but gave no figures.

In the light of recent publications concerning the treatment of epilepsy, it seems advisable to discuss briefly dehydration, ketosis and acidosis in diabetes and the factors influencing them. It is well known that persons with diabetes often become dehydrated, usually owing to lack of treatment. The patient in case 10785 entered the New England Deaconess Hospital with a glycosuria of 8.3 per cent. In the next four days his weight increased from 118½ to 125¼ pounds (53.7 to 56.8 Kg.), and the dryness of the skin and mouth disappeared. If the diabetes has advanced still further, ketosis occurs with the excretion of acetone bodies through the kidneys and the lungs. Sometimes even then there is no appreciable lowering of the carbon dioxide-combining power of the plasma (case 11020), although often there is. As the ketosis increases, the carbon dioxide-combining power decreases, until at times it descends as low as 1.1 volumes per cent (Olmstead, quoted by Joslin, 1928). Diabetic treatment combats and eventually overcomes these three conditions. The carbon dioxide-combining power rises, the ketosis disappears, and soon the patient appears healthy without signs of dehydration. As a matter of fact, I have seen no reports concerning the carbon dioxide-combining power of the plasma in properly treated diabetic persons during the insulin era. Of course, prior to insulin therapy, mild ketosis and acidosis existed for long periods in some diabetic persons, even in those given the best of treatment, and almost all the children died in coma in spite of treatment. However, this is no longer true.

Persons with epilepsy, on the other hand, seem to have no evidence of dehydration, ketosis or disturbance of the acid-base equilibrium of the body fluids during the interparoxysmal periods. Lennox and Cobb (1928) referred to "the polyuria which frequently succeeds a convulsion," but they apparently attribute it to the accumulation of acid substances produced by the muscular work of the convulsion. In our cases

we have noted no such polyuria and no change in the weight of the patients at such a time, possibly because we have made no special study of this phenomenon. Ketosis apparently has not been noted in epileptic persons under ordinary conditions, and, except in evident acidosis, was present in only 7 of our cases. This ceased with treatment. There are, however, many observations on the acid-base equilibrium in epilepsy. Lennox and Cobb, in 1928, summarized the literature up to that time, and concluded that the acid-base balance is essentially normal between seizures, although there may be an abnormal degree of variation from day to day. Lennox (1928) found the carbon dioxide-combining power of the plasma within normal limits in 88 of 100 epileptic persons and above 70 volumes per cent in 12. Claude and Raffin (1928) found slight alkalinity preceding the attacks. Shera (1928) found no decrease and possibly some increase in the alkali reserve without regard to the attacks. We have made determinations of the carbon dioxide-combining power of the plasma in 8 of our patients without obvious diabetic acidosis. The values ranged from 47 to 54 volumes per cent, with an average of 50.6 volumes per cent. During diabetic acidosis the value in 1 case was 24 volumes per cent. Four other patients have at one time or another been definitely acidotic; 2 of them have been in coma.

#### TREATMENT

None of our epileptic patients have received any treatment for the epilepsy except the administration of sedatives. Phenobarbital was used in 10 cases with some benefit. Bromides apparently afforded relief in 2 cases. Thyroid extract was given in case 3019, as much for the patient's general condition as for any other reason. At first this seemed to decrease the epileptic attacks, but later the disease progressed markedly.

Since the papers of Guelpa and Marie (1910), Geyelin (1921) and Wilder (1921), there have been many publications<sup>3</sup> about fasting, ketogenic dietary regimens and dehydration in epilepsy. The observations of many workers<sup>4</sup> help to explain the benefit of these regimens so frequently noted in epilepsy. However, some studies<sup>5</sup> of the subject

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3. Hoeffel and Moriarty (1924); Shaw and Moriarty (1924); Talbot, Metcalf and Moriarty (1927); Peterman (1927 and 1928); Lennox and Cobb (1928); Lennox (1928); Geyelin (1929); McQuarrie (1929); McQuarrie and Husted (1929); Higgins (1930); Talbot (1930); Helmholz and Keith (1930); Barborka (1930); Fay (1930); Doolittle (1931); Bridge and Iob (1931).

4. Weir, Larson and Rowntree (1922); Gamble, Ross and Tisdall (1923); Rowntree (1926); Lennox (1928); Lennox, Nelson and Beetham (1929); Gamble (1929); Bridge and Iob (1931); McQuarrie and Peeler (1931).

5. Peterman (1927); Nelson (1928); McQuarrie (1929); Higgins (1930); Barborka (1930); Guthrie (1930); Gr  r (1930); Regan (1931).

have attributed minor deleterious effects to these methods of treatment. On the other hand, Talbot (1930) found that the ketogenic diet caused no disturbance of normal growth and development, and Higgins (1930), Helmholz (1932) and Clark (1932) expressed the belief that such a diet helps to overcome infection.

One might suppose that diabetic persons with epilepsy would be especially favorable subjects for such regimens, because in former years fasting and ketogenic diets were the accepted mode of treatment for diabetes, and the disease itself would enhance the results obtained. Yet many of the large diabetic clinics have abandoned the diet low in carbohydrates and high in fats. Such a diet is obtained with some difficulty, is not generally so satisfying to the patients as one containing at least 100 Gm. of carbohydrate, and seems more prone to cause languor and lassitude. There is good evidence that it induces hypercholesteremia, and it is considered in this clinic to be a predisposing cause of the premature arteriosclerosis so often seen in diabetic persons.

We have not thought it wise to use a ketogenic diet. Reference has been made to the disadvantages of this treatment. Furthermore, it seems unsafe to keep a person acidotic who not infrequently becomes severely acidotic and who might die, as others have, from such an acidosis. To a dehydration regimen a similar objection may be made, though the risk is less. However, there may be cases which should be made exceptions on account of uncontrolled epilepsy. Uncontrolled severe diabetes very simply accomplishes the results of both treatments, and yet I dislike to recommend neglect of one serious disease because of another.

#### SUMMARY AND CONCLUSIONS

1. The literature on convulsions attributed to diabetes or to its treatment has been reviewed, and pertinent data have been collected from our diabetic patients and set forth. 2. The evidence so far tends to discredit the idea that diabetes per se causes convulsions, but it is equally evident that excessive administration of either alkali or insulin may give rise to such seizures. 3. The appropriate literature concerning idiopathic epilepsy in persons with diabetes has been analyzed and correlated, and observations on our 22 cases have been added. 4. The incidence of epilepsy in diabetic persons seems to be similar to the theoretical incidence in unselected people of corresponding age groups.

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# TOXIC CIRRHOSIS CAUSED BY CINCHOPHEN

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Shortly after the introduction of cinchophen into the therapeutic armamentarium, patients revealing toxic effects were observed, and their cases were reported in the literature. In 1922, Schroeder<sup>1</sup> reported a series of cases, and urged caution in the use of the drug. In 1923, Worster-Drought<sup>2</sup> first reported the occurrence of jaundice as a toxic manifestation. The toxic symptoms are of various types: cutaneous, anaphylactoid, gastro-intestinal, cardiac, renal and hepatic. An extensive review of the question of the toxicity of cinchophen is being prepared by our colleague, Dr. Hench.<sup>3</sup> In this paper we are concerned only with cases in which there were hepatic manifestations. We have been able to find 98 cases reported in the literature, exclusive of those previously reported from the Mayo Clinic. The latter cases, together with others reported now for the first time, total 19, in 5 of which the results were fatal. This gives a total of 117 cases; in 61 the patients died, and in 45 necropsy was performed. This paper is a study of the clinical features of these cases so far as the data available are concerned, with particular reference to the cases from the clinic; we personally have cared for the majority of the latter patients.

Cinchophen (2 phenyl-quinoline, 4 carboxylic acid) was introduced by Nicolaier and Dohrn<sup>4</sup> in 1908 as an agent in the treatment of gout. Although its efficacy in the removal of tophi was not substantiated by clinical experience, its effect on purine metabolism was soon proved. The analgesic effect was also notable, and it soon was extensively used in place of salicylates for relief from pain caused by various rheumatic conditions. This was in part to escape the unpleasant effects

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1. Schroeder, K.: Cases of Cinchophen Poisoning, *Ugesk. f. læger* **84**:1141 (Sept. 7) 1922.

2. Worster-Drought, Cecil: Atophan Poisoning, *Brit. M. J.* **1**:148 (Jan. 27) 1923.

3. Hench, P. S.: Derivatives of Cinchophen and Their Toxicity, *Proc. Staff Meet., Mayo Clin.* **7**:427 (July 20) 1932.

4. Nicolaier, Arthur, and Dohrn, Max: Ueber die Wirkung von Chinolin-carbonsäuren und ihrer Derivate auf die Ausscheidung der Harnsäure, *Deutsches Arch. f. klin. Med.* **93**:331, 1908.

of salicylism. In 1923, Brugsch and Horsters<sup>5</sup> demonstrated the cholagogic effects of cinchophen on animals and on patients with biliary fistulas. An increase occurred in both the fluid and the total solid content of the bile. However, after large doses or after administration over a long period, both the fluid and the solid content fell below normal after the initial increase. Brugsch and Horsters interpreted this as being due to injury of the hepatic cells. Later, however, Brugsch<sup>6</sup> maintained the innocuous properties of the drug, and recommended its use in the treatment of subacute yellow atrophy of the liver. Other investigators similarly have demonstrated a cholagogic effect, and Traubman<sup>6</sup> stated that cinchophen is excreted in the bile. Thus it has been used in various forms; for example, as icterosan it has been used in the treatment of catarrhal jaundice and other hepatic conditions.<sup>7</sup>

In view of these facts, it was a logical step when Pribram<sup>8</sup> introduced biloptin (diiodo-cinchophen) in 1926 as a cholecystographic medium. Einhorn and Stewart and Einhorn, Stewart and Ryan<sup>9</sup> introduced it in America in 1927. Spurling and Hartman<sup>10</sup> reported on the effect of tolysin (neocinchophen) as an adjunct to iso-iodokon (phenyl-tetra-iodophenolphthalein sodium) in cholecystography. The administration of 15 grains (1 Gm.) of tolysin an hour before giving iso-iodokon apparently increased the rate of elimination of the dye. From further experiments Spurling and Hartman felt that possibly the phthalein compound produced some hepatic injury. However, on reviewing their tables one is impressed with the probability that the injury is due to the effects of the tolysin. In 1931, Lichtman<sup>11</sup> advocated the use of oxycinchophen as a determinant of hepatic function. If hepatic lesions are present, increased amounts of this compound are excreted in the urine.

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5. Brugsch, Theodor, and Horsters, Hans: *Cholere und Choleretika*, ein Beitrag zur Physiologie der Galle, *Ztschr. f. d. ges. exper. Med.* **38**:367, 1923.

6. Quoted by Davis.<sup>12</sup>

7. (a) Dassen, Rodolfo: *Sobre la acción hepatotóxica de los derivados de la fenilquinoleina*, *Semana méd.* **36**:368 (Feb. 14) 1929. (b) Nathorf and Willert, quoted by Adler, A.: *Therap. d. Gegenw.* **67**:174 (April) 1926. (c) Weiss, Samuel: *Acute Yellow Atrophy of the Liver: Acute Necrosis of the Liver*, *M. J. & Rec.* **135**:316 (April 6) 1932.

8. Pribram, quoted by Einhorn, Stewart and Ryan.<sup>9b</sup>

9. (a) Einhorn, Max, and Stewart, W. H.: *On Hepatography*, *M. J. & Rec.* **126**:430 (Oct. 5) 1927. (b) Einhorn, Max; Stewart, W. H., and Ryan, E. J.: *Experiences with Biloptin (Diiodoatophan) for Cholecystography by Oral or Duodenal Method*, *ibid.* **125**:457 (April 6) 1927.

10. Spurling, R. G., and Hartman, E. E.: *Serum-Colorimetry and Other Evidence of the Choleretic Action of Tolysin (Ethyl Ester of Paramethyl-Phenylcinchoninic Acid) in Man*, *J. Lab. & Clin. Med.* **13**:854 (June) 1928.

11. Lichtman, S. S.: *Cinchophen Oxidation Test of the Function of the Hepatic Cells*, *Arch. Int. Med.* **48**:98 (July) 1931.

Cinchophen is marketed in many forms, and many derivatives have been prepared. The quinoline radical is the essential nucleus of all these preparations. Hench listed a large series of such forms in which cinchophen is available. Unfortunately, it has not always been given under medical supervision. Moreover, it has been used by physicians without adequate knowledge of its dangers. Recently a patient presented himself giving a history of painless jaundice for five weeks following the use of oxyliodide (cinchophen hydroiodide) for arthritis. His physician had urged exploration for cholecystitis. The laity has learned of its analgesic effects and has purchased at drug stores large amounts of it and of patent medicines the active principle of many of which is largely cinchophen.

Chief of the various preparations which contain cinchophen are atophan (cinchophen) and oxyliodide. Other preparations, some of which have been mentioned, are biloptin, icterosan, neocinchophen, atoquinol (allyl phenylcinchoninicester), atophanyl (cinchophen sodium, sodium salicylate and procaine hydrochloride), quinophan (cinchophen), farastan (mono-iodo-cinchophen), Harrell's, Van Ard's and Cass' preparations, Gorum cachets and Renton's hydrocine tablets. There are many preparations on the market following the use of which cases of toxic cirrhosis have not been reported, but as Hench has pointed out, since estimates as to the total quantity of each preparation consumed are not available, conclusions as to their relative toxicity cannot be drawn. Further, as pointed out later, all cases are not reported, and others are not recognized.

Various hypotheses have been advanced as to the cause of the toxic symptoms, namely: breaking free of the benzene nucleus or the formation of toxic nitrocompounds from the quinoline nucleus; an impure form of the drug; an increased susceptibility of the liver from injuries such as alcoholism, eclampsia, cholecystitis, cirrhosis, starvation and undernutrition; other lesions producing jaundice; chronic infections generally, and sensitization of the liver from the administration of foreign protein. It is fairly definitely demonstrated that certain persons have an idiosyncrasy to the drug. However, the recent statement of Davis<sup>12</sup> seems justified: "No explanation at present exists for the toxicity of cinchophen except hypothesis."

Experimental work also has failed to solve the problem of toxicity. Most investigators have failed to produce hepatic injury in animals by the use of cinchophen. We know of only one investigator (Biberfeld<sup>13</sup>) who has reported such experimental injury; he produced toxic

12. Davis, J. S., Jr.: The Relation of Neocinchophen to the Question of Cinchophen Toxicity, *Am. J. M. Sc.* **184**:555 (Oct.) 1932.

13. Biberfeld, J.: Zur Wirkungsweise des Atophans, *Ztschr. f. exper. Path. u. Therap.* **13**:301, 1913.

cirrhosis in a dog after the administration of 75 grains (5 Gm.) of cinchophen. The explanation may be that only some animals, just as only some human beings, are susceptible to the drug.

On account of these reported effects of cinchophen, various suggestions have been made as to the proper method of administration of the drug to avoid toxic results. Thus, it has been urged that the drug be given three times a week; that soda be given simultaneously; that the intake of water be high; that dextrose be given freely first, to saturate the liver with glycogen, thus enabling it to resist the effects of a toxin; that iodine be not given simultaneously, and that the derivative neocinchophen (ethyl ester of *para*-methylphenylcinchoninic acid) be used. However, in spite of these precautions, toxic jaundice continues to occur.

#### CASES REPORTED ELSEWHERE THAN FROM THE MAYO CLINIC

In 1923, Worster-Drought reported the case of a man, aged 59, with chronic gout, who had used cinchophen in doses of  $7\frac{1}{2}$  grains (0.5 Gm.) three times daily for twelve days; urticaria developed and then cleared. Three weeks later, after another dose of cinchophen, urticaria recurred, and in ten days jaundice developed and did not clear for several weeks. The icterus was of moderate degree, and enlargement or tenderness of the liver was not demonstrable.

In 1925, Cabot and Cabot<sup>14</sup> reported the case of a man, aged 42, who had never been strong since the occurrence of typhoid fever in his youth. He had indefinite pains in his arms and legs for several years, and fatigue and weakness for one year. In the preceding two months he had used 3 packages of Weldona. Dull, burning retrosternal pain and belching developed, and were followed by progressive jaundice. Vomiting followed, and later edema and ascites. After vomiting much blood the patient became irrational and comatose, and died about six weeks after the onset of jaundice. At necropsy esophageal varices were found. The liver weighed 780 Gm., and had undergone yellow atrophy.

In 1926, Brown<sup>15</sup> (details given by Graham<sup>16</sup>) reported 2 cases.

CASE 1.—A woman, aged 69, had used 170 grains (11 Gm.) of cinchophen weekly for ten weeks for pains in the joints. Anorexia, vomiting and then jaundice developed. The jaundice deepened; the patient became very ill, and died on the eighth day. At necropsy the liver was small and was the site of advanced chronic hepatitis.

CASE 2.—A woman, aged 36, used atquinol in varying doses for five months for infectious arthritis, taking in all about 2,330 grains (151 Gm.). Jaundice developed, and death occurred ten days after her dismissal from the hospital. Necropsy was not made.

14. Cabot, R. C., and Cabot, Hugh: Case Records of Massachusetts General Hospital: Case 11231; Acute Yellow Atrophy, Boston M. & S. J. **192**:1122 (June 4) 1925.

15. Brown, W. L.: Atophan Derivatives in Rheumatism: A Caution, Brit. M. J. **2**:37 (July 3) 1926.

In 1927, Graham<sup>16</sup> reported the case of a woman, aged 63, who had used 150 grains (9.75 Gm.) of atophan weekly for rheumatoid arthritis. After three months she began to vomit, but continued to take the drug up to within three weeks before her death. Jaundice was present the last four days and coma the last two days. At necropsy the liver was small and revealed the presence of severe chronic hepatitis.

In 1926, Evans<sup>17</sup> reported 3 cases, but did not give the age and sex of the patients. Jaundice developed after 225 grains (15 Gm.) of atophan had been taken by each. In the first case jaundice recurred after from 7½ to 15 grains (0.5 to 1 Gm.) of atophan had been taken. All the patients recovered.

In 1926, Glover<sup>18</sup> reported the case of a woman, aged about 60, who received 38.5 cc. of atophanyl intravenously in varying amounts and at varying intervals for arthritis. Jaundice developed five days after the last injection and cleared in one month.

In 1926, Willcox<sup>19</sup> reported the case of a man, aged 69, who used 5 grains of atophan (0.3 Gm.) three times a day for a week for chronic gout. In a few days rapidly deepening jaundice developed, which persisted until the patient's death, twenty-eight days later. The terminal symptoms were those of icterus gravis. No mention was made of necropsy. Two other cases of jaundice occurring after the use of atophan, with recovery of the patients, were cited by Willcox, but he did not give further details.

In 1926, Wells<sup>20</sup> reported the case of a woman, aged 63, who, as treatment for arthritis, used twenty 7½ grains (0.5 Gm.) tablets of atophan weekly for from four and a half to five months. After three months of medication, vomiting developed, but the woman continued to use the drug until three weeks before her death. Jaundice was present only the last four days, and coma developed two days before death. At necropsy the liver was small and shrunken, and yellow atrophy was present.

In 1926, Klinkert<sup>21</sup> reported 2 cases, and in 1927,<sup>22</sup> 1 case.

CASE 1.—A woman with acute polyarthritis was given 5 cc. of atophanyl daily for fifteen days. Three days later, atophan was given three times a day for one month. On account of some abdominal pain, the medicine was omitted for a few days and then given twice daily for one month. A total of 166 tablets was taken. Malaise, anorexia and biliuria then developed. The liver was enlarged. The patient recovered.

16. Graham, George: The Treatment of Gout, *Proc. Roy. Soc. Med. (Sect. Therap. & Pharmacol.)* 20:1 (Jan.) 1927.

17. Evans, Geoffrey: Atophan Derivatives in Rheumatism, *Brit. M. J.* 2:93 (July 10) 1926.

18. Glover, L. G.: Atophan-Derivatives in Rheumatism, *Brit. M. J.* 2:136 (July 17) 1926.

19. Willcox, W. H.: Atophan Derivatives in Rheumatism, *Brit. M. J.* 2:273 (Aug. 7) 1926.

20. Wells, C. J. L.: Atophan Derivatives in Rheumatism, *Brit. M. J.* 2:759 (Oct. 23) 1926.

21. Klinkert, D.: Gelbsucht als Folge längeren Gebrauchs von Atophan, *Therap. d. Gegenw.* 67:334, 1926.

22. Kinkert, D.: Gelbsucht als Folge längeren Gebrauches von Atophan, *Klin. Wchnschr.* 6:24 (Jan. 1) 1927.

CASE 2.—A woman, aged 55, took 140 tablets of atophan, following which anorexia and urobilinuria developed, which lasted for one month, but biliuria did not result, and the patient recovered.

CASE 3.—A man, aged 60, with acute polyarthritis, took 160 tablets of atophan (1,200 grains, or 80 Gm.). A month later painless jaundice developed and rapidly deepened, but it finally cleared in two and a half months. The liver was palpable and slightly tender.

In 1927, Kingreen<sup>23</sup> reported the case of a woman, aged 31, who had biliary colic for two years and a small tumor below the liver, which was enlarged. She was given 75 grains (5 Gm.) of biloptin intravenously for cholecystography. The following day cholecystectomy for subacute cholecystitis without stones was performed. Two days later jaundice was noted, and vomiting occurred. The jaundice became deep, but finally cleared in a month.

In 1927, Hitzenger<sup>24</sup> reported two cases.

CASE 1.—A man, aged 21, with diabetes insipidus was given biloptin for cholecystography because of a complaint of tenderness at the right costal margin. The next day jaundice developed and progressed, and was associated with vomiting, convulsions and coma. Death occurred on the tenth day. Necropsy revealed yellow atrophy of the liver and a tumor of the pituitary gland.

CASE 2.—A man, aged 60, had been given biloptin for cholecystography because of a tumor in the right hypochondrium. The next day jaundice, anorexia, vomiting and pruritus developed. Recovery occurred in ten days.

In 1927, Schwartz<sup>25</sup> reported the case of a woman, aged 30, who received 75 grains (5 Gm.) of biloptin for cholecystography. Following this she complained of some gastric distress, and two days later vomiting and slight jaundice developed. Two weeks later, at the time of the report, the jaundice was deepening. The outcome was not given.

In 1927, Singer<sup>26</sup> reported the case of a woman, aged 56, who complained of vomiting, pain in the right portion of the abdomen and fever. On account of a mass in the right upper abdominal quadrant, biloptin was given for cholecystography. Several hours later severe vomiting began, and the following day jaundice was noticed. The next day hepatic dulness had diminished. During the next few days the jaundice lessened, but later pneumonia developed, and death occurred sixteen days after the administration of biloptin. At necropsy recurring ulcerative mitral endocarditis with hemorrhagic nephritis was found. Death was caused by endocarditis, but it was felt that the jaundice was due to biloptin.

In 1927, Haudek<sup>26</sup> reported the case of a man, aged 30, who received biloptin for cholecystography on account of distress in the region of the gallbladder. This was followed by nausea, vomiting and jaundice. Recovery occurred in three weeks.

In 1927, Rake<sup>27</sup> reported the case of a man, aged 54, who suffered from chronic alcoholism and gout, and who had used more than 1,500 grains (100 Gm.)

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23. Kingreen, Otto: Vorsicht bei der Verabreichung von Dijodatophan (Biloptin), *Deutsche med. Wchnschr.* 1:971 (June 3) 1927.

24. Hitzenger, K.: Acute Leberatrophie nach Biloptin, *Wien. klin. Wchnschr.* 40:205 (Feb. 17) 1927.

25. Schwartz, G.: Schweren Ikterus nach "Biloptin," *Wien. klin. Wchnschr.* 40:238 (Feb. 17) 1927.

26. In discussion on Schwartz.<sup>25</sup>

27. Rake, G. W.: A Case of Subacute Yellow Atrophy Following the Taking of Atophan, *Guy's Hosp. Rep.* 77:229 (April) 1927.

of atophan. One month before Rake saw the patient, sharp pain in the epigastrium had appeared and had been followed by slight jaundice, which had deepened and then gradually cleared. The clinical diagnosis was gallstones. Following another attack of gout, 10 grains (0.65 Gm.) of atophan was given on two days, and vomiting and diarrhea followed. Exploration revealed a small and irregularly shaped liver. No gallstones were found, and the abdomen was closed. Death occurred on the third day after operation. The liver weighed 1,150 Gm. and revealed evidence of necrosis and regeneration.

In 1927, de Rezende<sup>28</sup> reported 3 cases.

CASE 1.—A woman, aged 52, used 1,875 grains (125 Gm.) of atophan for rheumatic pains. Painless jaundice developed and persisted for six weeks. Following the subsequent intravenous injection of atophanyl, icterus of mild degree returned, but the patient recovered.

CASE 2.—A man had used atophan in small amounts, and intense jaundice and marked loss of weight occurred. He recovered in forty days.

CASE 3.—A woman, aged 52, with sciatica of the left leg used from 20 to 40 capsules of atophan (270 grains, or 18 Gm.). Later more atophan was used, and jaundice developed. The patient recovered in one month.

In 1928, Rabinowitz<sup>29</sup> reported 2 cases.

CASE 1.—A man, aged 33, began to use atophan following the extraction of a tooth, and took 1,500 grains (100 Gm.) in three months. Three weeks after the conclusion of the three months nausea, anorexia and weakness developed, and a week later, painless jaundice, which later became intense. The concentration of bilirubin was as high as 38 mg. in each 100 cc. of serum, but within two months after the jaundice had first appeared it had decreased to 3 mg. The patient recovered.

CASE 2.—A man, aged 39, suffered from "cold in the back." Following the use of 25 tablets of atophan, each of 7½ grains (0.5 Gm.), nausea, and three days later, jaundice and weakness developed. The concentration of bilirubin was 13 mg. in each 100 cc. of serum; in two and a half weeks it decreased to 2.5 mg. The patient recovered in one month.

In 1928, Weil<sup>30</sup> reported the case of a man, aged 47, who used atophan in unknown amounts, following which jaundice developed, the duration of which was not given. Necropsy revealed the presence of yellow atrophy. The pathologist felt that undernutrition was a factor in the development of the jaundice.

In 1928, Klinkert<sup>31</sup> reported the case of a woman, aged 65, who used 4 tablets of atophan daily for a total of 900 grains (60 Gm.) for rheumatic pain. This was followed by anorexia and jaundice of five weeks' duration. The patient recovered.

In 1928, Lowenthal, Mackay and Lowe<sup>32</sup> reported 2 cases.

28. de Rezende, Cassio: Rheumatismo atophan e ictericia, *Brasil-med.* **41**:1005 (Sept. 24) 1927.

29. Rabinowitz, M. A.: Toxic Hepatitis and Hepatolysis Following the Use of Atophan, *M. Clin. North America* **11**:1025 (Jan.) 1928.

30. Weil, Paul: Leberatrophie nach Atophanbehandlung? Ein Obergutachten, *Med. Welt* **2**:257 (Feb. 18) 1928.

31. Klinkert, D.: Atophantherapie und Leber, *Therap. d. Gegenw.* **69**:140, 1928.

32. Lowenthal, L. J. A.; Mackay, W. A., and Lowe, E. C.: Two Cases of Acute Yellow Atrophy of the Liver Following Administration of Atophan, *Brit. M. J.* **1**:592 (April 7) 1928.



CASE 1.—A woman, aged 55, took  $7\frac{1}{2}$  grains (0.5 Gm.) of atophan daily for six months because of arthritis (2,700 grains, or 175.5 Gm.). Deepening jaundice, delirium and coma then developed. The woman died six days after the onset of jaundice. Necropsy revealed yellow atrophy of the liver; the organ weighed 538 Gm.

CASE 2.—A woman, aged 55, who had rheumatic pain received  $7\frac{1}{2}$  grains (0.5 Gm.) of atophan three times a day over a period of about two months, or a total of 540 grains (35.1 Gm.). Two weeks later rapidly progressive jaundice developed, with some tenderness over the gallbladder. On account of the uncertain diagnosis, exploration was made, and a small cirrhotic appearing liver was found. Death occurred the next day, three weeks after the onset of jaundice. Necropsy revealed yellow atrophy, and the liver weighed 744 Gm.

In the London letter<sup>33</sup> in *The Journal of the American Medical Association*, the case was reported of a woman, aged 55, who received atophan three times daily for three weeks, a total of 525 grains (35 Gm.). After five weeks of jaundice, death occurred. Necropsy revealed yellow atrophy.

In 1928, Sutton<sup>34</sup> reported the case of a woman, aged 27, who used atophan for arthritis (75 tablets). This was followed by weakness, nausea, vomiting, edema, ascites and jaundice of eight weeks' duration. Necropsy disclosed yellow atrophy.

In 1929, Dassen<sup>7a</sup> reported 2 cases.

CASE 1.—A woman, aged 29, received an unknown amount of cinchophen and sodium salicylate for rheumatic fever. Two days later sore throat with phlegmon developed, and then jaundice became noticeable. The patient gradually recovered.

CASE 2.—A woman with mercurial toxic hepatitis and marked jaundice received atophanyl intravenously, which markedly aggravated the jaundice. Recovery was slow, but was complete in three months.

In 1929, Motzfeldt<sup>35</sup> reported the case of a woman, aged 27, who received 1,755 grains (117 Gm.) of cinchophen in two periods for two months. Jaundice developed, but the patient recovered slowly in two months.

In 1929, Braun<sup>36</sup> reported the case of a woman, aged 55, who received 5 cc. of atophanyl intravenously daily for twenty-five days. This was followed by jaundice, ascites, edema and enlargement of the liver. Recovery occurred; the duration of the illness was not given.

In 1929, Frenzel<sup>37</sup> reported the case of a man, aged 55, who used from 5 to 7 tablets, each of  $7\frac{1}{2}$  grains (0.5 Gm.), of atophan a day for two days (about 90 grains, or 6 Gm.). Marked weakness, emotional disturbance and loss of voice developed, and on the following day jaundice appeared. Later all of these symptoms gradually disappeared, and in three weeks the patient recovered.

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33. London Letter: The Danger of Atophan, J. A. M. A. **90**:1229 (April 14) 1928.

34. Sutton, D. C.: Acute Yellow Atrophy of the Liver Following the Taking of Cinchophen: Report of a Case, J. A. M. A. **91**:310 (Aug. 4) 1928.

35. Motzfeldt, K.: Cinchophen and Jaundice, Norsk mag. f. lægevidensk. **90**:283 (March) 1929.

36. Braun, L. I.: Jaundice with Ascites, Due to Intravenous Atophanyl Injections, J. M. A. South Africa **3**:157 (March 23) 1929.

37. Frenzel, W. C.: Liver: Subacute Yellow Atrophy Due to Cinchophen Poisoning: Report of a Case, Wisconsin M. J. **28**:264 (June) 1929.

In 1929, Anderson and Teter<sup>38</sup> reported the case of a woman, aged 48, who received 600 tablets of oxyliodide, of 3 grains (0.2 Gm.) each, in eight months, following which edema, jaundice, ascites and albuminuria developed. She became irrational, convulsions occurred, and death ensued. Necropsy revealed yellow atrophy and a liver weighing 450 Gm. The duration of the jaundice was not stated, but it was probably less than a month.

In 1929, Reichle<sup>39</sup> reported 2 cases.

CASE 1.—A woman, aged 20, on account of acute arthritis used cinchophen for three or four months, which was followed by jaundice, with recovery after six weeks. A month later, on account of the recurrence of the arthritis, she used 80 tablets of cinchophen,  $7\frac{1}{2}$  grains (0.5 Gm.) each, and 40 tablets of oxyliodide; still later she took 60 grains (4 Gm.) of cinchophen. The symptoms included fever, nausea, vomiting, diarrhea, bleeding from the nose and gums, pain in the thorax, apathy, weakness, emaciation, a macular cutaneous rash, jaundice and coma. The liver and spleen were enlarged. At necropsy the liver weighed 1,950 Gm., and yellow atrophy was present.

CASE 2.—A woman, aged 46, with arthritis used cinchophen in large amounts, 3,150 grains (204.75 Gm.) in 1926, 2,100 grains (136.5 Gm.) in 1927, and 1,800 grains (117 Gm.) in 1928. Epigastric pain, tenderness, weakness and jaundice developed; later edema, confusion, muscular twitching, convulsions and coma ensued. Death occurred after jaundice of ten or twelve days' duration. Necropsy revealed yellow atrophy and a liver weighing 757 Gm.

In 1929, Liedberg<sup>40</sup> reported 2 cases.

CASE 1.—A man, aged 60, used 338 grains (22.5 Gm.) of atophan in three weeks, which was followed by nausea, malaise and jaundice. The liver was enlarged. During the first week, the jaundice increased. This subsequently decreased, with recovery in four weeks.

CASE 2.—A woman, aged 63, used 3 tablets of atochinol daily for six weeks for arthritis. Two days after beginning medication, dark urine was noticed. Later dyspepsia, vomiting and jaundice developed. Recovery occurred in one month.

In 1930, Fink<sup>41</sup> reported the case of a man, aged 47, who used  $7\frac{1}{2}$  grains (0.5 Gm.) of cinchophen four times daily for arthritis (a total of 180 grains, or 12 Gm.). Three weeks later urticaria developed, and a week later painless jaundice with marked pruritus and purpura developed. The liver was slightly tender. The concentration of bilirubin was 7.5 mg. in each 100 cc. of serum. The jaundice cleared in ten days.

In 1930, Tak<sup>42</sup> reported the case of a man, aged 45, who received 150 grains (10 Gm.) of atophan. Later he took another 45 grains (3 Gm.), which was followed by anorexia, enlargement of the liver and jaundice. Recovery occurred in six weeks.

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38. Anderson, S. D., and Teter, D. P.: Acute Yellow Atrophy of the Liver Following Administration of Oxyl Iodide, *J. A. M. A.* **93**:93 (July 13) 1929.

39. Reichle, H. S.: Toxic Cirrhosis of Liver Due to Cinchophen, *Arch. Int. Med.* **44**:281 (Aug.) 1929.

40. Liedberg, Nils: Atophan Icterus, *Hygiea* **91**:801 (Dec. 15) 1929.

41. Fink, A. I.: Cinchophen Poisoning in Allergic Individuals: Report of Two Cases, *J. Allergy* **1**:280 (March) 1930.

42. Tak, P.: Dangers of Atophan, *Nederl. tijdschr. v. geneesk.* **74**:1744 (April 5) 1930.

In 1930, Rabinowitz<sup>43</sup> reported 7 cases.

CASE 1.—A woman, aged 37, used 360 grains (24 Gm.) of cinchophen for two months for rheumatic pains in the feet. Jaundice developed and persisted for two months. The patient recovered.

CASE 2.—A woman, aged 31, used 150 grains (10 Gm.) of atophan for two or three weeks. Weakness and jaundice developed, and because of this complication in the presence of pregnancy, therapeutic abortion was done. The liver was enlarged. The patient recovered from the jaundice in seven weeks.

CASE 3.—A man, aged 45, received  $7\frac{1}{2}$  grains (0.5 Gm.) of atophan three times daily for four or five months. He lost much weight, and jaundice developed. Ascites was present, and death occurred ten days later. Necropsy revealed portal cirrhosis and a liver weighing 1,100 Gm.

CASE 4.—A woman, aged 51, received 450 grains (30 Gm.) of atophan during four weeks. Pain in the abdomen, edema, jaundice and coma developed. Death occurred in four or five days. Necropsy revealed the presence of yellow atrophy.

CASE 5.—A woman, aged 26, received  $67\frac{1}{2}$  grains (4.5 Gm.) of atophan for pains in the joints, and jaundice developed after tonsillectomy. Later, hyperpyrexia was present. Death occurred ten days after the onset of jaundice. Necropsy was not performed.

CASE 6 (also reported by Grolnick<sup>44</sup>).—A woman, aged 45, used Weldon in two courses for about two weeks. This was followed by backache, belching, epigastric distress, diarrhea and malaise, and later by jaundice, which persisted for five weeks. Recovery occurred.

CASE 7.—A woman, aged 39, used atophan in large amounts for six months. Progressive jaundice developed. Exploration was made, and the patient died on the operating table. Necropsy revealed that the liver was small and cirrhotic.

In 1930, Lambert<sup>45</sup> reported the case of a man who used Harrell's rheumatism cure in large amounts for from one and a half to two years for rheumatic pains. This was followed by anemia, jaundice of unstated duration and death. Necropsy was not mentioned.

In 1931, Parsons and Harding<sup>46</sup> reported 4 cases.

CASE 1.—A woman, aged 65, used Van Ard's rheumatism cure for four months (700 grains or 45.5 Gm. of cinchophen) for chronic arthritis. Progressive weakness, malaise and nausea developed. Vomiting, bloody diarrhea and edema of the ankles were later symptoms. The duration of the jaundice was not known, but it was present one week before death. Coma developed, and death occurred four weeks after the first symptoms. At necropsy yellow atrophy was present, and the liver weighed 450 Gm.

CASE 2.—A woman, aged 67, had three mild attacks of jaundice during the use, in unknown amounts, of Van Ard's rheumatism cure for a general "bad feeling." Weakness, headache, nausea, vomiting, progressive jaundice and coma developed. Death occurred on the seventh day after the onset of jaundice. Necropsy revealed that the liver weighed 720 Gm., and yellow atrophy was present.

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43. Rabinowitz, M. A.: Atrophy of the Liver Due to Cinchophen Preparations, *J. A. M. A.* **95**:1228 (Oct. 25) 1930.

44. Grolnick, Max: Toxic Hepatitis Due to Cinchophen Containing Patent Medicine, *M. J. & Rec.* **132**:240 (Sept. 3) 1930.

45. Lambert, Alexander, in discussion on Rabinowitz.<sup>43</sup>

46. Parsons, Lawrence, and Harding, W. G., Jr.: Cinchophen (Atophan) Poisoning: Report of Four Cases, *Am. J. M. Sc.* **181**:115 (Jan.) 1931.

CASE 3.—A woman, aged 40, used atophan (1,950 grains or 127 Gm.) for six months because of rheumatism. Epigastric pain, nausea, vomiting, edema, marked jaundice and localized convulsions developed. Death occurred on the eighth day. Necropsy revealed yellow atrophy and a liver weighing 735 Gm.

CASE 4.—A woman, aged 46, used Cass' rheumatism cure in unknown amounts for an unknown period because of arthritis. Malaise, mild jaundice which progressed, nausea, vomiting and confusion developed. Death occurred on the ninth day after the onset of symptoms. At necropsy the liver weighed 700 Gm.

In 1931, Walker<sup>47</sup> reported 2 cases.

CASE 1.—A man, aged 43, used 96 grains (6.24 Gm.) of cinchophen for post-traumatic pain in the leg. A month later anorexia and epigastric distress developed, and in a few days vomiting and jaundice. These symptoms progressed, coma developed, and death occurred eleven days after the onset of jaundice. Necropsy revealed that the liver weighed 850 Gm. and that yellow atrophy was present.

CASE 2.—A woman, aged 59, six months before the presenting illness had used 750 grains (48.75 Gm.) of cinchophen on account of arthritis. Because of recurring pains, she again used cinchophen (30 tablets of 7½ grains each), which immediately produced heartburn, nausea and anorexia. A week later jaundice, persistent vomiting and drowsiness developed. After another week the liver seemed to decrease in size, and there was some epigastric tenderness. The jaundice deepened, the patient became delirious and stuporous, and edema developed. Death occurred two weeks after the onset of jaundice. At necropsy the liver weighed 650 Gm.; necrosis of the hepatic cells with regeneration was also noted.

In 1931, Ross<sup>48</sup> reported 5 cases.

CASE 1.—A woman, aged 42, used unknown amounts of tolysin intermittently for pains in the joints and muscles. A month later a severe digestive upset occurred, with pain, vomiting and fever, followed by jaundice. The vomiting continued, and there was evidence of a decreased area of hepatic dullness, delirium, ascites and petechial hemorrhages. Death occurred two months after the onset of jaundice. Necropsy revealed that the liver weighed 670 Gm., and that necrosis and regeneration were present.

CASE 2.—A woman, aged 58, used quinophen in doses of from 10 to 15 grains (0.65 to 1 Gm.) daily for several weeks on account of attacks of digestive disturbance and epigastric tenderness. Then a severe attack of indigestion and vomiting occurred, followed by jaundice, which persisted. One month and two months later similar attacks occurred, and after the last attack a mass was found at the right costal margin. At operation the gallbladder, which contained stones, was removed, and the common bile duct was drained. Death occurred twelve hours later, two months after the onset of jaundice. At necropsy the liver weighed 750 Gm.; necrosis of the hepatic cells with some regeneration was found.

CASE 3.—A man, aged 41, with tuberculosis of the right hip of two years' duration, used cinchophen and tolysin intermittently for three months. Death occurred

47. Walker, W. G.: Cinchophen and Acute Yellow Atrophy of the Liver: Report of Two Cases, *New England J. Med.* **204**:253 (Feb. 5) 1931.

48. Ross, J. B.: Liver Damage Following Cinchophen Preparations, with a Report of Five Cases, *Canad. M. A. J.* **24**:632 (May) 1931.

forty-eight hours after operation on the hip. There was evidence of a decreased area of hepatic dullness, but jaundice was absent. Necropsy revealed that the liver weighed 1,220 Gm., and was necrotic.

CASE 4.—A man, aged 26, took neocinchophen irregularly for two weeks for pains in the joints and muscles. During the last three weeks he had lost weight and had become slightly jaundiced; glycosuria developed, which eventually disappeared. Recovery occurred in from four to five months.

CASE 5.—A man, aged 68, used  $7\frac{1}{2}$  grains (0.5 Gm.) of atophan three times a day. A total of 855 grains (55 Gm.) was taken. This was followed by slight digestive disturbance, vomiting and jaundice. He recovered in from one to two weeks.

In 1931, Sherwood and Sherwood<sup>49</sup> reported the case of a man, aged 27, who used 75 grains (5 Gm.) of atophan for arthritis of possibly gonorrheal origin. Five days later mild jaundice developed, which cleared in one month.

In 1931, Willcox<sup>50</sup> reported 4 cases.

CASE 1.—A man, aged 35, used 2 tubes of atophan for from six to eight weeks. A month later deep jaundice developed, which persisted until recovery two months later.

CASE 2.—A man, aged 69, used 5 grains (0.3 Gm.) of atophan three times a day for six days. Three weeks later jaundice and enlargement of the liver developed. Death occurred about four weeks after the onset of jaundice. Necropsy was not mentioned.

CASE 3.—A woman, aged 20, used Gorum cachets twice daily for six days. Three weeks later rapidly deepening jaundice developed; five weeks later ascites was noted, and three weeks later severe hematemesis occurred, with death in two days, two months after the onset of jaundice. Necropsy was not mentioned.

CASE 4.—A woman, aged 52, used Gorum cachets three times a day intermittently for five weeks. A month later rapidly deepening jaundice developed, associated with vomiting and an enlarged liver. Recovery occurred in two months.

In 1931, Cabot<sup>51</sup> reported the case of a woman, aged 71, who used farastan for several weeks on account of arthritis. This caused diarrhea. Weakness, edema, ascites and slight icterus developed. Death occurred about ten days after the development of edema. Necropsy revealed a liver weighing 800 Gm. and the characteristic picture of yellow atrophy.

In 1931, Eimer<sup>52</sup> reported the case of a man, aged 52, who used 1,770 grains (118 Gm.) of atophan during forty days for subacute arthritis. A month after he began to use the drug, malaise, anorexia, slight jaundice and fever developed. Later petechiae developed, associated with marked deepening of the jaundice, enlargement of the liver and general apathy. Recovery occurred in seven weeks.

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49. Sherwood, K. K., and Sherwood, H. H.: Acute Toxic Hepatitis (Acute Yellow Atrophy) Due to Cinchophen: Report of a Case, *Arch. Int. Med.* **48**:82 (July) 1931.

50. Willcox, William: Toxic Jaundice, *Lancet* **2**:57 (July 11) 1931.

51. Cabot, R. C.: Case Records of Massachusetts General Hospital: Case 17291; Four Months' Pain in the Legs and Five Days' Edema Below the Waist, *New England J. Med.* **205**:153 (July 16) 1931.

52. Eimer, Karl: Atophanvergiftung und ihre Behandlung, *Deutsche med. Wchnschr.* **57**:1663 (Sept. 25) 1931.

In 1931, Bogen<sup>53</sup> reported the case of a girl, aged 19, who received  $7\frac{1}{2}$  grains (0.5 Gm.) of cinchophen three times a day for five weeks (825 grains or 55 Gm.) on account of arthritis of the ankle. Nausea, vomiting and discomfort in the right upper quadrant of the abdomen developed, and a week later definite jaundice was noted. The concentration of bilirubin was 15 mg. in each 100 cc. of serum. A week later, on account of severe pain in the right side of the abdomen, nausea, vomiting and leukocytosis, exploration of the abdomen was undertaken under spinal anesthesia. Aside from a distended stomach, the findings were negative. Death occurred in five days, twelve days after the onset of jaundice. Necropsy revealed a necrotic liver weighing 1,200 Gm.

In 1931, Elliot<sup>54</sup> reported the case of a woman, aged 24, who used 126 grains (8.4 Gm.) of oxyliodide for a stiff, painful shoulder; nausea, vomiting, rapidly deepening jaundice, mental confusion and coma developed. Hallucinations, disorientation and Babinski reflexes were present. Death occurred on the twelfth day after the onset of symptoms. Necropsy was not mentioned.

In 1932, Gargill<sup>55</sup> reported 2 cases.

CASE 1.—A woman, aged 47, received 84 grains (5.6 Gm.) of oxyliodide for chronic arthritis. Moderate pruritus developed; later anorexia and nausea appeared, and two weeks later jaundice developed. The liver was enlarged, and the concentration of bilirubin was 26 mg. in each 100 cc. of serum. Recovery occurred in two months.

CASE 2.—A woman, aged 47, used 432 grains (28.8 Gm.) of atophan and oxyliodide in two weeks for pain in the left leg. One week later pruritus, anorexia, nausea and jaundice were noted. The liver was enlarged. The patient recovered in three months.

In 1932, Lind<sup>56</sup> reported the case of a woman, aged 39, who following the extraction of a tooth took from 10 to 12 tablets ( $7\frac{1}{2}$  grains or 0.5 Gm. each) of cinchophen. This was followed by weakness, and five weeks later gradually deepening jaundice developed. A week later still the jaundice decreased, and then ascites developed for which paracentesis was required on three occasions. Death occurred five weeks after the onset of jaundice. Necropsy revealed yellow atrophy of the liver, which weighed 750 Gm.

In 1932, S. Weiss<sup>7c</sup> reported 3 cases in which acute necrosis of the liver developed after the use of icterosan (10 per cent atophan) for advanced jaundice. The age and sex of the patients are not given.

In 1932, C. R. Weis<sup>57</sup> reported 3 cases.

CASE 1.—A man, aged 26, used 60 grains (4 Gm.) of atophan daily for three months because of rheumatic pains following tonsillitis. Jaundice developed, associated with nausea, vomiting, edema, lethargy and delirium. Death occurred

53. Bogen, Emil: Cinchophen Poisoning: Report of Case, California & West. Med. **35**:269 (Oct.) 1931.

54. Elliot, A. H.: Toxic Cirrhosis of the Liver from "Oxyl-Iodide": Report of Case, J. A. M. A. **97**:1384 (Nov. 7) 1931.

55. Gargill, S. L.: Cinchophen Poisoning: A Report of Three Cases, New England J. Med. **206**:183 (Jan. 28) 1932.

56. Lind, S. C.: Report of a Case of Acute Yellow Atrophy of the Liver Due to the Use of a Small Amount of Cinchophen, Ohio State M. J. **28**:28 (Jan.) 1932.

57. Weis, C. R.: Toxic Cirrhosis of the Liver Due to Cinchophen Compounds: Report of Three Fatal Cases, J. A. M. A. **99**:21 (July 2) 1932.

after three weeks. Necropsy revealed yellow atrophy of the liver; the organ weighed 680 Gm.

CASE 2.—A man, aged 65, used 60 grains (4 Gm.) of atophan daily for four months for arthritis. Weakness, anorexia, nausea and drowsiness developed, followed in a few days by vomiting and jaundice. Later on, edema, delirium and coma developed. Death occurred about three weeks after the onset of symptoms. At necropsy there was necrosis of the liver with some signs of regeneration.

CASE 3.—A woman, aged 64, used 4 tablets of farastan daily for four months on account of arthritis. Nausea, vomiting, anorexia, weakness and rapidly deepening jaundice developed. Death occurred about two weeks after the onset of symptoms. Necropsy revealed a small, extensively necrosed liver.

In 1932, Berger and Schweid<sup>58</sup> reported 2 cases.

CASE 1.—A woman, aged 63, used 540 grains (35 Gm.) of cinchophen for arthritis. A digestive upset, slight pain in the upper quadrant of the abdomen and jaundice developed. The jaundice increased, and was associated with a decrease in the size of the liver, pruritus, drowsiness and muscular twitching. Six weeks later her condition was much improved. Exploration was undertaken because of a mass in the right upper abdominal quadrant. Peritonitis with death followed. At necropsy the liver weighed 940 Gm., and yellow atrophy was present.

CASE 2.—A man, age unknown, used 1,417 grains (92 Gm.) of cinchophen in three weeks, which was followed by rapidly deepening jaundice, a decrease in the size of the liver, muscular twitching and coma. Necropsy was not reported.

In 1932, Reah<sup>59</sup> reported 3 cases.

CASE 1.—A woman, aged 64, used 588 grains (38 Gm.) of cinchophen at intervals. This was followed by nausea, anorexia, vomiting, jaundice, pruritus and giddiness. Death occurred twenty-five days after the onset of jaundice. Necropsy revealed red atrophy of the liver.

CASE 2.—A man, aged 63, used 60 grains (4 Gm.) of cinchophen because of gout. Fifteen weeks later abdominal pain, vomiting and jaundice developed. Coma and death followed three weeks after the onset of jaundice. At necropsy the liver was found to be small, with extensive necrosis.

CASE 3.—A woman, aged 39, used 7 grains (0.45 Gm.) of cinchophen three times daily for two months. Severe pain in the lower part of the abdomen, vomiting, headache, thirst and jaundice developed. The patient recovered.

In 1932, Parsons and Harding<sup>60</sup> reported 6 cases.

CASE 1.—A woman, aged 64, used Renton's hydrocine, 6 tablets daily for six months (5,400 grains or 351 Gm. of cinchophen). This was followed by deep jaundice, a decreasing area of hepatic dulness, slight edema and distention of the abdomen. Four months later, marked ascites, edema and distention of the superficial abdominal veins developed. Paracentesis was necessary on several occasions. Six weeks later omentopexy and posterior gastro-enterostomy were performed for pyloric obstruction. Death occurred in three days, six months after the onset of jaundice. Necropsy was not made.

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58. Berger, S. S., and Schweid, H. H.: Cinchophen Poisoning in a Diabetic with Induction of Hypoglycemia, *M. J. & Rec.* **136**:50 (July 20) 1932.

59. Reah, T. J.: Cinchophen Poisoning, *Lancet* **2**:504 (Sept. 3) 1932.

60. Parsons, Lawrence, and Harding, W. G., Jr.: Fatal Cinchophen Poisoning: Report of Six Cases, *Ann. Int. Med.* **6**:514 (Oct.) 1932.

CASE 2.—A man, aged 70, used 45 tablets of Renton's rheumatism remedy in a month (225 grains or 14.6 Gm. of cinchophen) because of rheumatism. Much pruritus developed; later progressive weakness, loss of weight, jaundice and a decreasing area of hepatic dulness with tenderness appeared. The symptoms progressed, and death occurred four weeks after the onset of jaundice. Necropsy was not made.

CASE 3.—A woman, aged 64, used 12 tablets of Renton's hydrocine for arthritis. Three months later jaundice associated with decreasing hepatic dulness developed, which later was followed by coma. The concentration of bilirubin was 25 mg. in each 100 cc. of serum. Death occurred two weeks after the onset of jaundice. Necropsy revealed a necrotic liver weighing 500 Gm.

CASE 4.—A man, aged 56, used atophan for three or four weeks because of pain in the foot. Generalized pruritus developed and then subsided. Six months later jaundice, weakness and anemia developed. The jaundice subsided for a time, but recurred. Death occurred more than six months after the use of the drug. Necropsy was not made.

CASE 5.—A man, aged 62, used 6 tablets of atophan daily for three weeks on account of neuritic pains in the legs. This was followed by urticaria and marked jaundice, which progressed and led to death. The duration of the jaundice was not given, and necropsy was not performed.

CASE 6.—A man, aged 43, used 200 of Renton's hydrocine tablets in a period of six months (1,000 grains or 65 Gm. of cinchophen) for arthritis of the hips. Epigastric distress, tenderness, vomiting and rapidly deepening jaundice occurred. The symptoms progressed to a fatal outcome. The duration of the jaundice is not given. At necropsy a necrotic liver weighing 780 Gm. was found.

In 1932, Davis<sup>12</sup> reported 3 cases.

CASE 1.—A woman, aged 45, received atophan and neocinchophen in large doses for a year because of infectious arthritis. Jaundice developed and death occurred in a few days. Necropsy was not made.

CASE 2.—A girl, aged 17 years, with a history of catarrhal jaundice two years previously, received 10 grains (0.65 Gm.) of tolysin four times daily, or a total of 700 grains (45.5 Gm.), because of infectious arthritis. Jaundice of a rapidly progressive type developed three weeks after she started to use the drug, and was associated with delirium and hyperpyrexia. Death occurred in eight days. Necropsy was not performed.

CASE 3.—A patient, age and sex unknown, received cinchophen and potassium iodide alternately. Three weeks later jaundice developed. Recovery occurred.

In 1932, MacGregor<sup>61</sup> reported the case of a man, aged 58, who had previously used alcohol heavily and had had diabetes mellitus for four years. On account of headache and painful joints and muscles, he was given 5 grains (0.3 Gm.) of neocinchophen three times a day (total amount unknown, but the prescription was filled several times). Jaundice developed and was associated with weakness, nausea, vomiting, drowsiness, restlessness and coma. Death occurred in ten days. Necropsy was not made.

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61. MacGregor, D. A.: Cinchophen Poisoning, Proc. Staff Conf., Wheeling Clin. 3:46 (Sept. 1) 1932.



## CASES FROM THE MAYO CLINIC

Group 1 is composed of cases in which there was no jaundice.

CASE 1.—A man, aged 66, registered at the clinic on July 6, 1932. He had had lumbago three or four times in the previous twelve years, and constant lumbar pain, with radiation into the posterior portion of both thighs, for which he had taken 4 or 5 boxes (each containing 24 tablets) of atophan in the previous four or five years, and 3 or 4 boxes (each containing 24 tablets) of cinchophen in the previous two or three years, with a great deal of relief. He had used only a little alcohol.

The lower edge of the liver was palpable 6 cm. below the costal margin; ascites and collateral veins were absent. The movements of the spine were limited. The concentration of bilirubin was 1.8 mg. in each 100 cc. of serum, and the van den Bergh reaction was indirect. The bromsulphthalein test of hepatic function revealed retention of dye, graded 3. The galactose tolerance test was negative. Roentgenologic examinations of the gallbladder revealed no abnormality; those of the spinal column gave evidence of hypertrophic changes in the lumbar portion. The diagnosis was toxic cirrhosis due to cinchophen and hypertrophic arthritis with sciatic pain. The patient was given a sacro-iliac belt and instruction in physical therapy. A diet high in carbohydrates was recommended, and he was advised not to use cinchophen and asked to return for reexamination. On November 16, the liver was definitely decreased in size, its surface was smooth, and its edge was soft. The retention of dye had diminished to grade 1, the concentration of bilirubin was 1.2 mg., and the van den Bergh reaction was indirect.

CASE 2.—A woman, aged 54, entered the clinic on July 4, 1932. For the previous ten years she had been treated for hypertension, indigestion and constipation. In April, 1932, she took 120 capsules of oxyiodide of 3 grains (0.2 Gm.) each because of rheumatic pain. The first of a series of attacks of weakness of several hours' duration, without change in the pulse rate, blood pressure, color, respiration or sweating, suddenly appeared three weeks previous to admission. Six days afterward an atypical attack of pain involved the entire abdomen.

On examination, the blood pressure in millimeters of mercury was 125 systolic and 80 diastolic, and a slight resistance in the right upper quadrant of the abdomen was noted. The retinal vessels gave evidence of hypertensive sclerosis, graded from 1 to 2. A galactose tolerance test and studies of the stools for parasites, ova and occult blood gave negative results. The electrocardiogram was normal. Roentgenograms of the stomach disclosed nothing significant; those of the gallbladder revealed that the organ was not functioning. The concentration of bilirubin was 2.3 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. The bromsulphthalein test of hepatic function disclosed a retention of dye, graded 4. The diagnosis was hypertension, arteriosclerosis, toxic cirrhosis due to cinchophen, and constipation. Possibly cholecystitis existed, but this did not explain satisfactorily the hepatic injury and other symptoms. The decision as to the advisability of operation was deferred until the results of the disappearance of the jaundice and the return of the hepatic function to normal had been observed. It was uncertain whether the attacks of weakness were an expression of myocardial degeneration or of disease of the liver. The patient was placed on a diet high in carbohydrates, including dextrose in large amounts, and was dismissed on July 26. The patient wrote on November 10, stating that she had gained weight, was much improved and felt well.

*Comment.*—Cases 1 and 2 represent latent or mild forms of toxic cirrhosis caused by cinchophen without visible jaundice. In case 1, the enlargement of the liver led to a search for etiologic factors, and a history of the use of the drug was obtained. No elevation of the concentration of bilirubin in the serum or change in the van den Bergh reaction was present. Hepatic injury was revealed by the enlargement of the liver and by the retention of dye. The decrease in the size of the liver, its softer consistence and the improvement in function as measured by the retention of dye, as noted on subsequent examination, served to confirm our original opinion that the diagnosis was toxic cirrhosis caused by cinchophen poisoning instead of portal cirrhosis. In case 2, a subclinical degree of icterus was present. Only after repeated questioning as to the cause of the weakness and peculiar abdominal symptoms was a history of the use of the drug elicited and laboratory evidence of hepatic injury obtained. The improvement with discontinuation of the drug and appropriate treatment indicates that not only cholecystitis, but likewise myocardial degeneration, was a relatively insignificant factor. Toxic cirrhosis due to cinchophen satisfactorily explains the syndrome. The danger of operation in such cases can be avoided only by careful consideration of all factors. Similar cases have been reported by Ross and Klinkert. In the case reported by Ross, an atrophied liver (1,220 Gm.) was found at necropsy; death had occurred after an operation on a tuberculous hip. Definite hepatic injury without jaundice had occurred. In Klinkert's case urobilinuria of thirty days' duration was noted. Jones<sup>62</sup> stated that he had seen 1 case of diffuse hepatic disease without jaundice, and 4 or 5 cases of yellow atrophy of unstated cause with ascites as a presenting symptom. Such cases definitely establish the fact that hepatic injury without jaundice occurs and presents clinical pictures capable of recognition which in many cases no doubt precede the more obvious phases of the disease. Certainly it is at the preicteric stage of toxic cirrhosis that a diagnosis is best made if much disability and permanent hepatic injury are to be avoided, and if complete functional and anatomic restoration is to be accomplished.

Group 2 is composed of cases in which there was mild jaundice.

CASE 3.—A man, aged 52, registered at the clinic on Sept. 29, 1930. For seven months he had suffered from pain in the left sacro-iliac region, with radiation into the region of distribution of the left sciatic nerve. Two months before admission his physician prescribed oxyliodide. Six weeks later jaundice came on gradually, and the administration of oxyliodide was promptly discontinued. During the two weeks before admission there was no evidence that the jaundice was decreasing.

Examination revealed slight icterus. The liver was slightly enlarged and tender. Examination of the spinal column revealed scoliosis, with list to the right, and

62. Jones, Chester, in discussion on Cabot.<sup>51</sup>

neurologically there was evidence of sciatic neuritis on the left side. The van den Bergh reaction was direct, and the concentration of bilirubin was 5.8 mg. in each 100 cc. of serum. When the patient was under treatment for sciatica, the jaundice cleared in two and a half weeks after admission; the concentration of bilirubin was 2.5 mg. in each 100 cc. of serum, and the van den Bergh reaction was still direct.

CASE 4.—A man, aged 52, registered at the clinic on Feb. 2, 1931, with the complaints of pains in the joints and jaundice. He had been a moderate user of alcohol, and during the previous nine years he had recurrent attacks of arthritis, which had left no residual changes. Three weeks before admission he had another attack and took 30 tablets of oxyliodide over a period of ten days. Shortly before admission his physician noticed a slight degree of jaundice. He had lost 7 pounds (3.2 Kg.), and he experienced considerable lassitude and weakness.

Examination revealed the presence of a mild grade of icterus. The liver, which was tender, extended 7 cm. below the xiphoid cartilage, and 5 cm. below the costal margin in the right mammary line. The spleen was not palpated. External evidence of previous arthritis was not visible. Roentgenograms of the gallbladder taken after the ingestion of dye revealed that it was not functioning. The concentration of bilirubin was 5.7 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. A bromsulphalein test of hepatic function revealed retention of dye, graded 4. The flow of bile by duodenal drainage was free, 180 cc. being obtained. On February 12, the concentration of bilirubin declined to 2.5 mg. in each 100 cc. of serum. The value for uric acid was 5.2 mg. for each 100 cc. of blood. A diagnosis of gout and toxic hepatitis caused by cinchophen poisoning seemed justified. Decision as to the disease of the gallbladder was deferred until the jaundice cleared, and further roentgenograms of the organ were taken. The patient was dismissed on February 15 on a diet high in carbohydrates with restriction of purines, and was advised to use salicylates and colchicum when necessary for gout. On October 28, roentgenograms of the gallbladder were made elsewhere after the intravenous administration of dye, and the organ was only faintly depicted. A diagnosis of cholecystitis was made, and cholecystectomy was performed on December 9. The surgeon reported that some pericholecystitis was found, as well as inflammatory changes in the mucosa. The significant changes were in the liver; it was almost normal in size, form and consistence, but had a nodular surface. There was distinct cirrhosis, which, however, had not progressed to the stage of producing portal obstruction.

CASE 5 (previously reported from the clinical standpoint by Snell and Jordan<sup>63</sup>).—A man, aged 42, registered at the clinic on July 15, 1929. Because of extensive infectious arthritis he had been taking a "rheumatic remedy" that contained cinchophen. Jaundice developed six months previous to examination and still persisted.

The patient was emaciated, moderately jaundiced (concentration of bilirubin, 4.6 mg. in each 100 cc. of serum) and rather badly disabled by infectious arthritis. The liver and spleen were palpable. Ample quantities of bile were secured by duodenal drainage. Discontinuation of treatment with arthritic drugs and a diet high in carbohydrates led to the slow disappearance of the jaundice and recovery from this feature of the illness.

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63. Snell, A. M., and Jordan, F. M.: Intrahepatic Jaundice, *Northwest Med.* 29:295 (July) 1930.

*Comment.*—Cases 3, 4 and 5 represent the milder grades of toxic cirrhosis caused by cinchophen. In case 4, the previous use of alcohol raises two questions of importance. Did the alcohol predispose to cinchophen poisoning, and did the alcohol rather than the cinchophen account for the pathologic changes in the liver observed at operation? It is impossible to answer the first question. With regard to the second question, it was observed that although the liver was of almost normal size and consistence, a nodular condition was present. This may be interpreted to mean that the condition was nodular hyperplasia without an obvious increase in connective tissue, a pathologic process at variance with that met in portal cirrhosis, but in keeping with our concept of toxic cirrhosis due to cinchophen. In our opinion, the pathologic changes are best accounted for by cinchophen poisoning, and represent a stage in the pathogenesis of toxic cirrhosis. The differential diagnosis between hepatic disease and cholecystitis in case 4 likewise illustrates some important points. The cholecystitis was too mild and the symptoms were too indefinite to warrant the belief that it was much of a factor in the genesis of the intrahepatic jaundice. The cholecystographic diagnosis of nonfunctioning gallbladder made at the time of the visit to the clinic must be discounted, for cholecystography is of limited value in the presence of jaundice or a diffusely diseased liver. A nonfunctioning gallbladder is often found to be functioning normally when the jaundice has cleared. A normally functioning organ, as indicated by cholecystography, is sometimes seen in the presence of slight jaundice or mild diffuse hepatic disease; in such instances, the test may be considered to have ruled out marked disease of the gallbladder and to have absolved the gallbladder of playing an important part in the causation of the jaundice.

In case 5, the jaundice was of long duration and mild, and it cleared rapidly when the administration of cinchophen was discontinued. The long duration probably depended on the continued administration of cinchophen. The patient evidently had only mild idiosyncrasy to the drug. Malnutrition may have been a predisposing factor that permitted development of the toxic cirrhosis. Few if any symptoms were produced by hepatic injury in cases 3 and 5, and the chief treatment indicated was discontinuance of the use of the drug.

Group 3 is composed of a case in which there was moderately severe jaundice.

CASE 6.—A woman, aged 53, first registered at the clinic on Sept. 16, 1929. Subtotal thyroidectomy was performed for exophthalmic goiter of five years' duration. There was no evidence of visceral degeneration. On December 14, the patient returned because of acute scleroderma in the edematous stage, which had developed one month previously. In August, 1930, arthritis appeared, and her physician prescribed cinchophen. Administration of this drug was continued for

five weeks, or until two nights before admission, when she was awakened by pain in the upper part of the abdomen.

The next day the patient was mildly icteric, and slight tenderness was present in the right upper quadrant of the abdomen; the fingers revealed arthritic deformities. The concentration of hemoglobin was 55 per cent. The urine contained tyrosine. The concentration of bilirubin was 10 mg. in each 100 cc. of serum. The retention of dye was graded 4 by the bromsulphalein test. A free flow of bile was obtained by duodenal drainage. Although cholecystography revealed a non-functioning gallbladder, this was disregarded because of the jaundice. The patient was placed on a diet high in carbohydrates; calcium lactate was given, and dextrose was administered intravenously. The concentration of bilirubin fluctuated between 11.5 and 14.9 mg. in each 100 cc. of serum until dismissal at the patient's request on September 29. The diagnosis was toxic cirrhosis caused by cinchophen. In October and November, 1931, an exacerbation of the scleroderma necessitated a return to the clinic, but there were no complaints referable to the liver.

*Comment.*—The condition of the patient in case 6 was moderately severe, without marked constitutional and mental symptoms. The jaundice was deeper and somewhat more prolonged than in the previous group. Digestive disturbances, including pain, were prominent, but under appropriate treatment the patient recovered. The degree and duration of the jaundice approximated those encountered in cases of catarrhal jaundice in which the patients seek hospitalization.

Group 4 is composed of cases in which the patients were convalescent.

CASE 7.—A woman, aged 65, entered the clinic on Jan. 20, 1931. She had been in good health, except for rheumatic pains, during the last few years, but had experienced an unexplained loss of 20 pounds (9 Kg.) in the preceding five months. About November 26 she began to take  $7\frac{1}{2}$  grains (0.5 Gm.) of cinchophen, three times daily, but this she discontinued at the end of two weeks, after two days' itching of the arms and legs. On December 17, jaundice, without associated chills, fever or pain, appeared, and reached a maximal degree in two days. The patient lost her appetite and was annoyed with belching and bloating. On December 23, she had a severe "gas pain" lasting two hours, with residual aching that lasted for two days, in the right upper quadrant of the abdomen. The jaundice began to improve ten days before the patient's admission to the clinic, and had virtually disappeared three days before, thirty days after the onset.

The sclera and skin were slightly icteric. A cholecystogram revealed that the gallbladder was functioning normally. The concentration of bilirubin was 1.7 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. The bromsulphalein test of hepatic function disclosed retention of dye, graded 2. The diagnosis was toxic cirrhosis due to cinchophen. The patient was dismissed on Jan. 23, 1931.

The woman registered again on May 4. No further trouble had been caused by the liver. The concentration of bilirubin was 1.7 mg. in each 100 cc. of serum, the van den Bergh reaction was indirect, and there was no retention of dye. She had had diarrhea, however, for the last three weeks, and proctoscopic examination revealed early chronic ulcerative colitis.

CASE 8 (previously reported from the clinical standpoint by Comfort<sup>64</sup>).—A man, aged 69, registered at the clinic on Feb. 2, 1932, with the complaint of painless jaundice of one month's duration. In December, 1931, because of arthritis he took 70 capsules of oxyliodide. On Jan. 3, 1932, painless jaundice with clay-colored stools and dark urine developed. The jaundice increased until about January 19, and then began to fade.

General physical examination gave essentially negative results with the exception of jaundice, a loss of 20 pounds (9 Kg.) and a slightly enlarged liver. There was a slight trace of bile in the urine. The concentration of bilirubin was 10 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. Duodenal drainage yielded a free flow of cloudy, amber-colored bile. On February 9, the concentration of bilirubin had dropped to 5 mg. in each 100 cc. of serum.

The patient was dismissed from observation on February 11 on a diet high in carbohydrate and low in protein, and calcium lactate in doses of 60 grains (4 Gm.) three times a day was given. On March 3, he reported that the jaundice had disappeared, and that his weight and strength were approaching normal.

CASE 9.—A man, aged 54, registered at the clinic on Dec. 5, 1932, with the complaint of jaundice of forty days' duration. In July, 1932, arthritic pains appeared in the spinal column, knees and elbows, and in September the patient began the use of 3 capsules of oxyliodide three times a day. On September 10, an attack of nausea, vomiting and diarrhea that lasted for twenty-four hours occurred. The oxyliodide was taken over periods of ten days with intervals of the same duration until October 20. On October 10, an infection of the upper portion of the respiratory tract apparently developed. On October 15, an urticarial rash appeared and lasted for two days. On October 23, there was a second attack of nausea and malaise. On October 25, jaundice appeared, and reached its greatest intensity within a few days. A cholecystographic examination at the height of the jaundice showed that the gallbladder was not functioning. The jaundice had been gradually clearing.

General physical examination gave negative results except for the presence of a slight grade of jaundice and a tender liver extending about 5 cm. below the costal margin on deep inspiration.

The bromsulphalein test of hepatic function revealed retention of dye, graded 2. The concentration of bilirubin was 1.6 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. Cholecystographic examination revealed that the gallbladder was functioning normally. Our diagnosis was toxic cirrhosis due to oxyliodide and arthritis. The patient was advised to continue the diet high in carbohydrates and to avoid cinchophen or any of its derivatives in the future. The foci of infection will be removed later, and physical therapy is to be continued. The patient was dismissed from observation on December 8.

*Comment.*—The three patients, cases 7, 8 and 9, presented themselves at the clinic after the stage of recovery had been well established. The course of their illness had been mild, of average duration (from thirty to forty days) and without mental symptoms. The relative mildness of the process in cases 7 and 9 is further attested to by the retention of dye, graded 2, at the end of the phase of jaundice, in contrast to the

64. Comfort, M. W.: Toxic Cirrhosis Due to Derivatives of Cinchophen: Report of Four Nonfatal Cases, Proc. Staff Meet., Mayo Clin. 7:419 (July 20) 1932.

higher grades of retention which persist in the more severe cases for even two or three months after the disappearance of jaundice. The possibility of obtaining normal cholecystograms in the presence of moderate diffuse hepatic disease is illustrated in cases 7 and 9. In these cases, no treatment other than the use of a diet high in carbohydrates and avoidance of further use of the drug seemed necessary.

Group 5 is composed of severe cases.

CASE 10 (previously reported from the clinical standpoint by Comfort).—A man, aged 64, came to the clinic on May 24, 1932, with the complaint of loss of weight and strength together with jaundice. Six weeks before admission he began taking Cass' rheumatism remedy for muscular pains. It was estimated that not more than 55 grains (3.5 Gm.) of cinchophen had been taken. On May 5, the urine was noticed to be darker than usual, and vomiting occurred occasionally. A week later the skin was definitely yellow, and thereafter the degree of jaundice increased rapidly. In the last two weeks before admission the patient had slept most of the time, and had lost 20 pounds (9 Kg.).

The patient was stuporous and very weak, the jaundice was intense, and the liver and spleen could not be palpated. The concentration of bilirubin was 25 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. The patient was placed on a diet high in carbohydrates and low in protein, and was given intravenously 1,000 cc. of a 10 per cent solution of dextrose and 1 per cent sodium chloride daily. On May 26, 27 and 30 and June 1, a large quantity of bile-stained fluid was obtained by duodenal drainage, and after June 4 amber-colored bile was recovered from the duodenum, and the concentration of serum bilirubin fell, at first slowly, then rapidly. The urine contained no lead or arsenic. The galactose tolerance test disclosed 5.1 Gm. of reducing substance in the urine. On June 20, the margin of the liver was barely palpable, and the galactose tolerance test revealed the presence of 2.15 Gm. of reducing substance. The patient's general condition had improved rapidly, and he was dismissed on a diet high in carbohydrates and low in protein, to which were added large quantities of dextrose and bread. The diagnosis was toxic cirrhosis caused by cinchophen poisoning.

On August 31, four months after the onset of jaundice, the condition of the patient was excellent; the liver was still barely palpable, the concentration of bilirubin was 1.2 mg. in each 100 cc. of serum, the van den Bergh reaction was indirect, the retention of dye was graded 2, and the gallbladder was functioning normally, as revealed by cholecystographic examination.

CASE 11 (previously reported from the clinical standpoint by Comfort).—A man, aged 46, registered at the clinic on Dec. 29, 1930. One year previously he noticed slight ataxia and paresthesia of the legs, more marked on the left. The condition was partially relieved by the administration of 5 grains (0.3 Gm.) of cinchophen three times a day. The patient had taken a total of about 1,260 grains (82 Gm.) of the drug over a period of three months previous to his registration. Ten days previous to registration he noticed vague epigastric distress and soreness, jaundice, dark urine and clay-colored stools.

On admission the patient was deeply jaundiced, very weak and drowsy. The edge of the liver was palpable about 5 cm. below the right costal margin on deep inspiration, and was tender. The spleen was not palpated. The urine contained a moderate amount of albumin, bile and casts, but no lead or arsenic. The concentration of bilirubin was 15 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. A free flow of amber-colored bile was obtained on

repeated duodenal drainage. From January 1 to 17, the patient was given intravenous injections of from 150 to 500 cc. of 20 per cent solution of dextrose daily. When he was dismissed on January 29, the concentration of bilirubin was 4.3 mg. in each 100 cc. of serum. Weakness was still marked. The results of neurologic examination were indeterminate.

The patient returned for examination on April 8, his chief complaints being persistent weakness, gaseous abdominal distress, constipation and paresthesia of the legs. The liver and spleen were not palpated. The concentration of bilirubin was 2.2 mg. in each 100 cc. of serum, and the van den Bergh reaction was indirect. The bromsulphalein test of hepatic function revealed retention of dye, graded 2. The neurologic changes were essentially the same. By June 9 the patient's strength was much increased. The liver could just be felt at the costal margin. The bromsulphalein test of hepatic function disclosed retention of dye graded 1 and hepatic injury persisting six months after the onset of jaundice. On August 17, his general condition was excellent. The concentration of bilirubin was 1.4 mg. in each 100 cc. of serum, and the van den Bergh reaction was indirect. The retention of dye was graded 0.

CASE 12 (previously reported from the clinical standpoint by Comfort).—A man, aged 61, registered at the clinic on March 23, 1932. During the preceding six months, because of arthritis of the hip, he took Renton's rheumatic tablets, in an amount containing approximately 1,050 grains (68 Gm.) of cinchophen. Fourteen days before registration, jaundice, with dark urine and clay-colored stools, but without pain or pruritus, began. The degree of jaundice increased rapidly; the patient lost weight, strength and appetite, and he became slightly drowsy.

On admission, the patient was deeply jaundiced, and the liver was slightly enlarged and tender. A roentgenogram of the right hip disclosed slight thickening along the lower margin of the joint. The concentration of bilirubin was 15 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. On March 26, the concentration of bilirubin reached 17.8 mg. in each 100 cc. of serum. The galactose tolerance test revealed 3 Gm. of reducing substance in the urine. Daily injections of 1,000 cc. of 10 per cent dextrose and 1 per cent sodium lactate were given, and the concentration of serum bilirubin fell consistently. Large quantities of light amber-colored bile were obtained by duodenal drainage. The patient's strength and weight increased, and the liver became smaller. When he was dismissed on April 12, the concentration of bilirubin was 2.8 mg. in each 100 cc. of serum. A diagnosis of toxic cirrhosis secondary to poisoning by cinchophen was made. On April 27, the patient reported that he had almost completely recovered his strength and weight, and the jaundice had disappeared. On July 7, his condition was excellent, and the concentration of bilirubin was 1.5 mg. in each 100 cc. of serum. The van den Bergh reaction was indirect, but the bromsulphalein test of hepatic function revealed retention of dye graded 4. On Oct. 17, 1932, the edge of the liver descended to the costal margin on inspiration, and the concentration of bilirubin was 1 mg. in each 100 cc. of serum. That the function of the liver had not returned to normal after seven months was indicated by retention of bromsulphalein, graded 2.

CASE 13.—A woman, aged 60, was examined at the clinic on Aug. 8, 1932. She had had progressive rheumatic pains in the shoulders, arms and wrists from early winter until May, 1932. On May 14, her physician prescribed cinchophen, 5 grains (0.3 Gm.) four times a day, which she took for ten days, with relief from the pain. On May 27, urticaria appeared and persisted for one week. About



July 1 exhaustion, drowsiness and nausea developed, and she lost 10 pounds (4.5 Kg.). On August 1, jaundice was noticed, and on examination a week later this was very intense. There were associated anorexia and soreness in the upper part of the abdomen.

General physical examination revealed that the edge of the liver was easily palpable and soft. The concentration of bilirubin was 50 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct (fig. 1). The urine revealed the presence of bile and tyrosine, but otherwise was normal. The cholesterol content was 228 mg., and the cholesterol esters, 64 mg. in each 100 cc. of blood. Repeated determinations of galactose tolerance gave normal results except on one occasion when 4.22 Gm. of reducing substance appeared in the urine. This occurred during a mild relapse in the clinical condition.

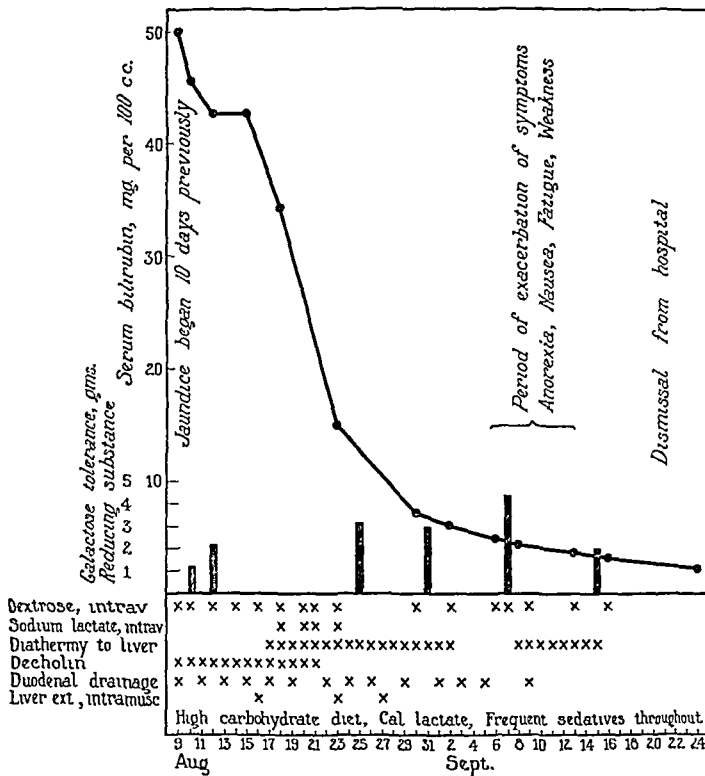


Fig. 1 (case 13).—Graphic representation of the serum bilirubin curve, galactose tolerance and therapeutic procedures.

Treatment consisted of a diet high in carbohydrates, repeated duodenal drainage, repeated intravenous injections of dextrose and salt solutions, the administration of calcium lactate by mouth, occasional intravenous injections of sodium lactate, diathermy over the hepatic region and occasional intramuscular injections of liver extracts. Gradually, clinical improvement resulted, with a coincident decline in the value for serum bilirubin except for a few days when the jaundice was nearly cleared, at which time, nausea, anorexia, weakness and exhaustion recurred. On October 13, the van den Bergh reaction was still direct, and the concentration of bilirubin measured 1.5 mg. in each 100 cc. of serum. The bromsulphalein test of hepatic function revealed retention, graded 2. The details of the laboratory data and treatment given are shown in figure 1. The patient remained under observation until November 1, at which time she felt well and was almost free from jaundice.

CASE 14 (previously reported from the clinical standpoint by Weir<sup>65</sup>).—A man, aged 56, registered at the clinic on Dec. 21, 1926. During the previous year he had suffered from sciatic pains in the right leg, and six weeks before admission his physician prescribed cinchophen. Two weeks afterward jaundice without pain or pruritus appeared, and two weeks later edema of the lower extremities and progressively increasing abdominal enlargement were noticed.

The patient was moderately jaundiced, the abdomen was tensely distended with fluid, and the legs were moderately edematous. The liver and spleen were not palpated. The urine contained bile. The concentration of bilirubin was 8.3 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. Diuresis followed the administration of ammonium chloride and merbaphen, and restriction of the intake of fluid and salt resulted in the disappearance of the ascites and edema and loss of 37 pounds (16.8 Kg.) before dismissal. At this time, six weeks after the onset of jaundice, the patient was almost free from jaundice, the concentration of bilirubin being 2.7 mg. in each 100 cc. of serum. In a letter dated Aug. 26, 1928, the patient reported that he was in good condition.

*Comment.*—In addition to the concentration of serum bilirubin, the mental symptoms, loss of strength and ascites act as reliable indexes of the intensity of the hepatic injury. In cases 10, 11, 12, 13 and 14, one or more of these conditions were present to a degree to warrant classification of the cases as examples of severe toxic cirrhosis. In all 5 cases, the extreme loss of strength and the general debility rendered the prognosis exceedingly grave on admission. The unfavorable prognosis was emphasized in case 10, and especially in case 13, by the depth of the concentration of serum bilirubin; in cases 10, 11 and 12, it was emphasized by the presence of mental symptoms to a degree that justified a fear of impending coma, and in case 14, by the presence of ascites. In case 10, the diet low in carbohydrates and calories imposed before admission had contributed to the seriousness of the patient's condition by causing a diminution in the glycogen reserve of the liver. The rapidity with which this patient responded to diet high in carbohydrates and to intravenous injections of dextrose was startling. Similar experiences with patients denied carbohydrates before admission have served to confirm clinically the experimental evidence of the value of dextrose in the treatment of hepatic injury, and have led us to believe that at least the duration of the disability is shortened and even death averted, as it may have been by such means in the foregoing cases in which jaundice was severe.

The duration of the jaundice was only slightly longer than in the cases in which the severity of the disease was moderate. However, further evidence of the severity of the condition is found in the prolonged period of retention of dye which followed the clearing of jaundice in cases 10, 11, 12 and 13. The retention of dye was graded 2 in

65. Weir, J. F.: The Association of Jaundice and Ascites in Diseases of the Liver, J. A. M. A. 91:1888 (Dec. 15) 1928.

1 case, and was graded 4 in another at the end of approximately four months. The retention of dye was graded 1 in case 11, five and a half months after the disappearance of jaundice, and was graded 2 in case 12, seven months after the disappearance of jaundice. The malaise and loss of strength usually disappeared within two months after the concentration of bilirubin in the serum approached normal; the patient apparently regained his health long before the functional rehabilitation of the liver was complete as indicated by the bromsulphalein test.

The galactose tolerance test was positive, or questionably so, in the 3 cases in which it was carried out, and served to confirm our clinical impression of diffuse hepatic injury.

The liver was palpable and presumably enlarged in cases 11, 12 and 13 and not palpable in cases 10 and 14. It is our impression that the liver is usually enlarged in nonfatal cases, and at necropsy the liver in the fatal cases, with one exception, was smaller than normal, often markedly diminished in size. The fact that a liver is not palpable in a case in which symptoms and other findings suggest a process of more than ordinary severity should increase the gravity of the prognosis. The opposite is not necessarily true, for a liver may be apparently enlarged and yet be found small at necropsy.

Ascites and jaundice together lend an especially bad prognosis to the case, and relatively few patients with such a combination recover. In the total group of 117 cases, ascites and jaundice were present in 13. The patient in case 14 and only 2 other patients recovered. In the usual case it is well to disregard the ascites and treat the liver energetically with every means at command. When the general condition has improved and the mental and nervous symptoms have disappeared, cautious use of diuretics may be attempted.

Group 6 is composed of fatal cases.

CASE 15 (previously reported from the pathologic standpoint by Beaver and Robertson<sup>66</sup>).—A man, aged 37, last registered at the clinic on Aug. 1, 1929. On March 13, 1923, partial thyroidectomy was performed because of exophthalmic goiter. At that time there was no evidence of hepatic injury. On Aug. 1, 1929, he returned to the clinic, stating that for the previous month he had been taking atophan, 3 tablets daily, on the advice of his physician, for chronic infectious arthritis. One week before admission he began to have chills, high fever and painless jaundice, which rapidly deepened and became associated with much weakness and vomiting.

On admission the patient was not mentally clear; he was drowsy, and slept a great deal. His memory was poor for details. The jaundice was moderate. The edge of the liver was not palpable. The concentration of bilirubin was 14.5 mg. in

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66. Beaver, D. C., and Robertson, H. E.: The Specific Character of Toxic Cirrhosis as Observed in Cinchophen Poisoning: A Review of Five Fatal Cases, *Am. J. Path.* 7:237 (May) 1931.

each 100 cc. of serum, and the van den Bergh reaction was direct. Our diagnosis was toxic cirrhosis due to cinchophen. On August 2, the patient became more confused and uncooperative, sleepy and restless. Death occurred on August 4, eleven days after the onset of jaundice. At necropsy the liver weighed 1,320 Gm., and the diagnosis was toxic cirrhosis.

CASE 16 (previously reported from the clinical standpoint by Stacy and Vanzant,<sup>67</sup> and from the pathologic standpoint by Beaver and Robertson).—A woman, aged 52, registered at the clinic in December, 1929. In 1922, she received treatment with radium at the clinic for epithelioma of the uterine cervix, from which she afterward had no trouble. In October, 1931, she began to take from 1 to 3 tablets of cinchophen daily for sciatic pain, but discontinued taking the drug after six weeks, when nausea and vomiting appeared. Jaundice without pruritus developed one week later, seven days before admission.

The jaundice was deep and bright orange-yellow. Nausea was the only other complaint. The liver was palpable, and the spleen was slightly enlarged. The concentration of bilirubin was 39 mg. in each 100 cc. of serum, and the van den Bergh reaction was direct. Bile was not obtained on duodenal drainage or in the stools. Treatment consisted of a diet high in carbohydrates, calcium lactate by mouth and calcium chloride and dextrose intravenously, both with and without insulin. The liver daily became smaller, and drowsiness, stupor and coma developed on the fourth day. Death occurred on the ninth day, sixteen days after the development of jaundice, with terminal hyperpyrexia and bronchopneumonia. At necropsy the liver weighed 904 Gm., and the typical gross and microscopic picture of acute yellow atrophy was noted. There was a recurrence of the malignant process in the pelvis with involvement of the sciatic nerves.

CASE 17 (previously reported from the clinical standpoint by Snell and Jordan<sup>63</sup> and Weir and Jordan,<sup>68</sup> and from the pathologic standpoint by Beaver and Robertson<sup>66</sup>).—A deeply jaundiced woman, aged 57, presented herself at the clinic on July 8, 1929. In February, 1929, after she had taken 9 capsules of oxyliodide prescribed by her physician for arthritis; administration of the drug was discontinued because of generalized pruritus. The itching then ceased. In April, 1929, the same symptoms followed the taking of only 1 powder, and the medication was again discontinued. During the latter part of May, 2 tablets of oxyliodide after each meal and at bedtime were prescribed, and the itching reappeared after 2 tablets had been ingested. On the advice of her physician use of the tablets was continued; anorexia and asthenia developed, and she lost from 10 to 15 pounds (4.5 to 6.8 Kg.) After approximately 250 tablets had been taken, their use was discontinued thirteen days before the patient's admission to the clinic, and progressively deepening jaundice developed two days later.

On examination, loss of weight, deep jaundice and arthritis of the hands were noted. The concentration of bilirubin varied from 30.4 to 44.4 mg. in each 100 cc. of serum. Duodenal drainage yielded only small amounts of clear, amber-colored bile. The patient's condition remained stationary until July 22, when nausea, vomiting and subcutaneous hemorrhages developed. An irrational, stuporous state rapidly changed into coma with hyperpyrexia. In spite of vigorous intravenous treatment with dextrose, death occurred on July 26, twenty-nine days after the onset of jaundice.

67. Stacy, Leda J., and Vanzant, Frances R.: Poisoning from Cinchophen, *Minnesota Med.* **13**:327 (May) 1930.

68. Weir, J. F., and Jordan, F. M.: Clinical Consideration of Some Types of Intrahepatic Jaundice, *M. Clin. North America* **13**:1439 (May) 1930.

At necropsy the liver weighed 640 Gm., and presented the typical picture of acute yellow atrophy. Numerous hemorrhages were noted throughout the body.

CASE 18 (previously reported from the clinical standpoint by McVicar and Weir,<sup>69</sup> and from the pathologic standpoint by Beaver and Robertson).—A woman, aged 37, registered at the clinic on April 19, 1928. Twelve months previously her first child was born; slight vomiting complicated pregnancy. Since that time she had been exhausted and annoyed by generalized aching, for which she took atophan. Four weeks before admission to the clinic nausea developed; later, itching was noticed, and two weeks before admission jaundice appeared. Epigastric pain was experienced two days before her arrival at the clinic. The concentration of bilirubin was 6 mg. in each 100 cc. of serum, and duodenal drainage revealed satisfactory secretion of bile. The jaundice cleared rapidly, and after a normal cholecystogram had been obtained the patient was dismissed on April 26, 1928.

About June 1, following an attack of nausea and vomiting, the jaundice reappeared, and when the patient was readmitted on July 10 the jaundice was deep. The concentration of bilirubin was 30 mg. in each 100 cc. of serum. Little bile was obtained by duodenal drainage. Prostration, anorexia and nausea were marked. An erythematous eruption, abdominal distention, edema and delirium appeared. Death, with a terminal fall in the concentration of bilirubin to 20 mg. in each 100 cc. of serum, occurred on July 29. At necropsy the liver presented gross and histologic evidence of acute toxic cirrhosis, and weighed 1,045 Gm. There was no evidence of disease in the gallbladder, bile ducts or pancreas.

CASE 19 (previously reported from the pathologic standpoint by Beaver and Robertson).—A man, aged 62, registered at the clinic in April, 1930. Five weeks previously there was pain in the left shoulder and the hands, for which he took oxyliodide on the advice of his physician, using 2 boxes of the capsules. His appetite, strength and weight began to fail. Three weeks before admission the urine became dark, and jaundice without pruritus developed.

Brilliant yellow icterus of moderate grade was present. The liver and spleen were not palpated. On April 29, 50 cc. of light amber-colored bile was recovered on duodenal drainage. Until May 8, the concentration of bilirubin was about 10 mg. in each 100 cc. of serum. On May 21, it diminished to 2.9 mg., and the van den Bergh reaction was direct. Our diagnosis was toxic cirrhosis due to cinchophen poisoning, and the patient was dismissed, with instructions that his diet should be high in carbohydrates.

The patient returned to the clinic on August 2, stating that he had improved somewhat after leaving the hospital. His jaundice had never cleared entirely, and he continued to be troubled with insomnia, weakness, anorexia and arthritis. He was moderately icteric. The concentration of bilirubin was 8.8 mg. in each 100 cc. of serum. The liver was definitely enlarged, and extended 2 cm. below the costal margin. On August 6, 50 cc. of light amber-colored bile was obtained by duodenal drainage. On August 12, the concentration of bilirubin reached 16.6 mg. in each 100 cc. of serum, the patient's condition grew worse, and respiration was slow. On August 26, the concentration of urea reached 60 mg. in each 100 cc. of blood, the stupor deepened into coma, and death ensued. At necropsy the liver weighed 1,134 Gm. and presented the picture of toxic cirrhosis. The peritoneal cavity contained 2,000 cc. of fluid.

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69. McVicar, C. S., and Weir, J. F.: Acute Yellow Atrophy, Possibly Due to Poisoning by Atophan, *M. Clin. North America* **12**:1526 (May) 1929.

*Comment.*—All of the patients in the fatal group (cases 15, 16, 17, 18 and 19) had used cinchophen or oxyliodide. Cases 15, 16 and 17 were of the fulminating type, and the drug had been used consistently for from one to two months. Weakness, anorexia, nausea and vomiting were the first symptoms, and progressed. Later, nervous features, apathy, drowsiness, delirium and coma developed, ending in death eleven, sixteen and nineteen days, respectively, after the onset of jaundice. The retention of bilirubin in the blood varied from 14.5 to 44.4 mg. In case 17 there was a progressive increase of the serum bilirubin. The liver was palpable in cases 16 and 19; in case 16 it decreased in size with the progress of the disease. It is worthy of note that pruritus was the first symptom in case 17, and that use of the drug was continued on the recommendation of the patient's physician. It is now known that administration of the drug should have been stopped promptly.

In the 2 chronic cases (18 and 19), after the patients apparently had made a preliminary recovery, relapses occurred and were possibly caused by further use of the drug. In case 18, the drug had been used intermittently for more than a year, and the relapse may have been caused by failure of the nodular hyperplasia to compensate fully for the previous chronic injury. Terminal symptoms of portal obstruction in the form of ascites and edema occurred in both of these cases. In case 19, a terminal rise in the serum bilirubin occurred, and in the other (18), a terminal fall.

Intensive treatment in these 5 cases had no effect in staying the fatal outcome. The marked asthenia shortly after the onset of jaundice, the persisting anorexia and nausea, the depth of the jaundice, in cases 15, 16 and 17, and the relapse, in cases 18 and 19, were definitely poor prognostic signs. Some of the patients in the other groups who recovered had jaundice as deep or deeper than that which occurred in the fatal cases, but the other symptoms were not prominent and recovery occurred, although the prognosis at first seemed doubtful.

#### PATHOLOGIC CHANGES

Necropsy was performed in the 5 fatal cases and in 40 of the 61 fatal cases reported in the literature, and in every case the liver was the organ most severely injured. It presented the picture of acute or sub-acute atrophy or of toxic cirrhosis. It varied in weight from 450 Gm. in the case of Anderson and Teter to 1,950 Gm. in the case of Reichle. Beaver and Robertson have pointed out that toxic cirrhosis due to cinchophen fulfils the three pathologic characteristics of toxic cirrhosis: (1) relatively rapid necrosis and autolysis of the hepatic parenchyma resulting in atrophy of the liver, (2) a relative increase of connective tissue which arises from parenchymal loss without much proliferative

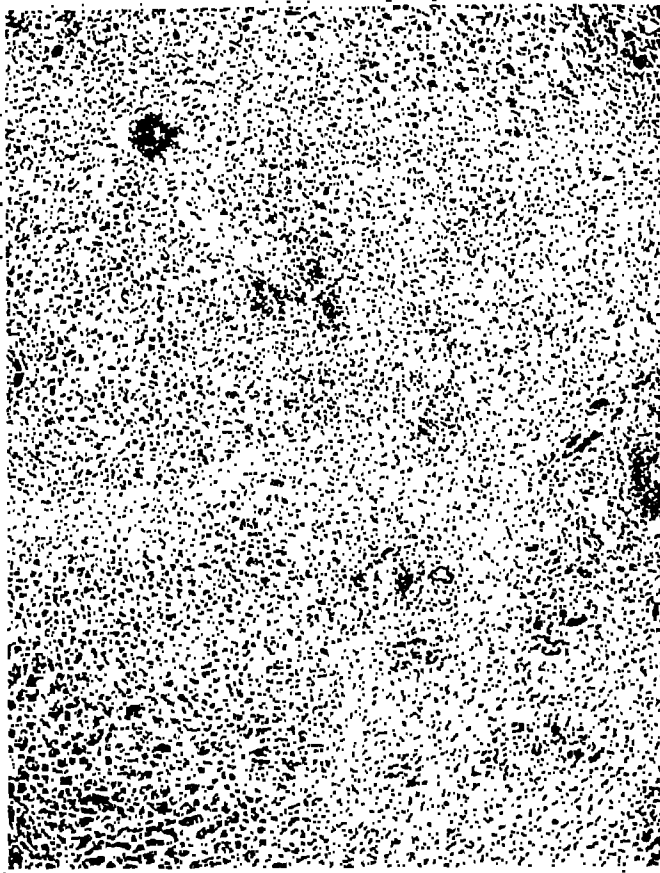


Fig. 2.—Acute stage: Extreme disorganization and necrosis of hepatic cells; congested sinusoids (hematoxylin and eosin;  $\times 65$ ).



Fig. 3.—Subacute stage: Complete dismantling of lobule following necrosis of hepatic cells. The cellular detritus has been cleared. The lobular sinusoids and reticulum are prominently displayed. Some sinusoids and the central vein are congested; other sinusoids with the reticulum are collapsed (hematoxylin and eosin;  $\times 120$ ).



Fig. 4.—Chronic state (early toxic cirrhosis): Compression of skeletonized lobule by growing parenchymal nodules, as revealed by silver impregnation method of Perdrau. A central vein is lying in compressed lobular stroma at the periphery of a regenerated nodule at the right (hematoxylin and eosin;  $\times 110$ ).

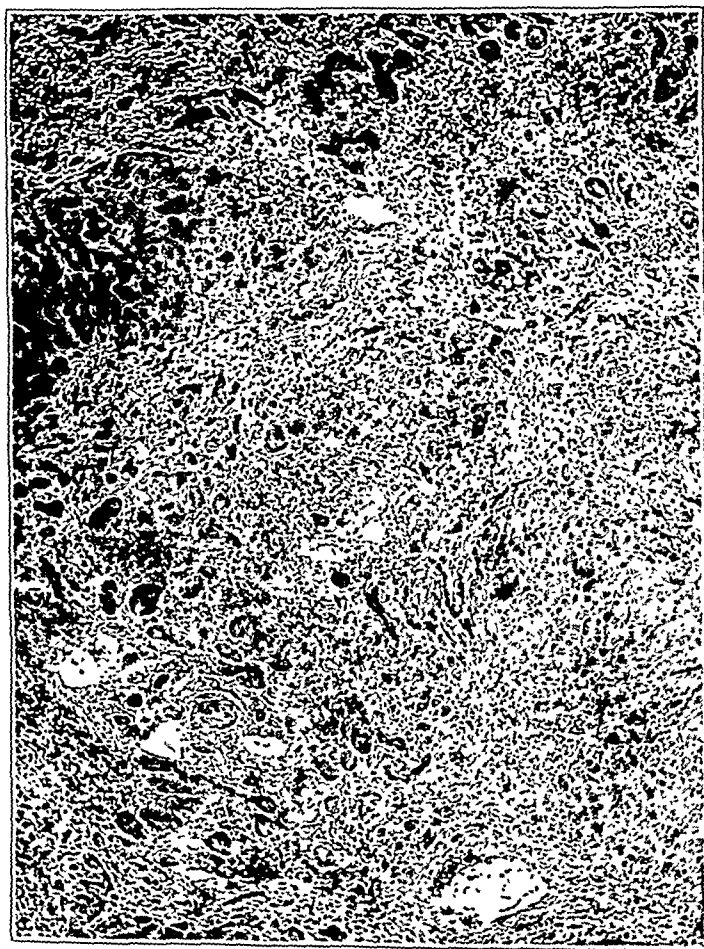


Fig. 5.—Chronic atrophy (early toxic cirrhosis): Nodules of regenerating hepatic cells. The hepatic stroma is shrunken, with sequential narrowing of the sinusoidal bed (hematoxylin and eosin;  $\times 65$ ).



reaction on the part of the connective tissue framework or the vascular apparatus of the liver and (3) regeneration predicted by the duration of life following the initial atrophy, arising as reformed nodules of the hepatic parenchyma from existent parts spared by the initial necrosis. The connective tissue shows somewhat more proliferation. Rabinowitz likewise felt that cirrhosis and nodular hyperplasia would result. Figures 2, 3, 4 and 5 show the various stages in the pathogenesis of the hepatic lesions.

The distinctive character of the pathogenesis in fatal cases has been confirmed by observers other than Beaver and Robertson. So far as we know there has been only 1 case in which the liver was examined after recovery from jaundice (our case 4). In that case, the surgeon described the liver as nodular, as of almost normal size and consistence and as presenting a picture of cirrhosis which, as we have pointed out, may be interpreted to mean nodular hyperplasia without an obvious increase in connective tissue—a pathologic process in keeping with our concept of toxic cirrhosis. Whether the regeneration and nodular hyperplasia are present in all nonfatal cases, or whether portal obstruction or hepatic insufficiency eventually will develop, can be settled only by further observation of the patients over a period of years.

#### GENERAL COMMENT

Although 98 cases of toxic cirrhosis from the use of cinchophen or preparations containing it (exclusive of those previously reported from the Mayo Clinic) have been reported in the literature, this does not represent all such cases. Thus, Rabinowitz stated that Kessel, in a personal communication, reported that he had seen 13 such cases. Bassler<sup>70</sup> stated that he had seen 9 cases, in 2 of which the results were fatal. Similar reports are given in the papers of Reichle and of Lind. Furthermore, there is a group of subclinical cases with definite hepatic injury. Thus, 1 of Ross' patients, 1 of Klinkert's patients and 2 of our patients did not reveal evidences of jaundice, and Cabot's second patient and Lind's patient had little jaundice. Undoubtedly many other cases have escaped detection. It is also possible that many of the other toxic manifestations, such as the cutaneous and anaphylactic features, may be associated with hepatic injury, for we see these symptoms in other types of hepatic disease. In passing, it is worthy of note that we have been unable to find any reports in the French literature.

The amount of the drug used varied in the cases in which the dosage was recorded, from 54 grains (3.6 Gm.) given in five weeks to 7,200 grains (480 Gm.) given in four months. An occasional fatal result

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70. Bassler, Anthony: Toxic Hepatitis due to Cinchophen, *J. A. M. A.* **99**:495 (Aug. 6) 1932.

followed the use of a very small amount of the drug, suggesting initial idiosyncrasy. In other cases, sensitiveness seemed to be acquired, as in de Rezende's first case. The drug was usually used continuously and seldom intermittently, as advised by Graham.

In the majority of cases, the cinchophen or some preparation of it was used for various types of arthritic, myositic or neuritic pains. Headache was an occasional reason. In 6 cases, biloptin was used for visualization of the gallbladder. In one of Dassen's cases, atophanyl was given intravenously for toxic hepatitis due to mercury, resulting in marked aggravation of the jaundice. In 3 cases cited by Weiss, acute necrosis followed the use of icterosan given for advanced jaundice. Nathorf and Willert saw apparently simple icterus turn into acute yellow atrophy

TABLE 1.—*Distribution of Cases According to Ages of Patients and Outcome of Disease*

Outcome of Disease	Patients in Different Decades of Life								Total
	Age Unknown	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	
Fatal.....	5	2	6	5	12	12	16	3	61
Nonfatal.....	9	..	4	8	8	13	13	..	55
Unknown.....	..	..	..	1	..	..	..	..	1
Total.....	14	2	10	14	20	25	29	3	117

TABLE 2.—*Distribution by Sex*

Sex	Cases of Disease with Given Outcome			
	Fatal	Nonfatal	Unknown	Total
Male.....	21	26	..	47
Female.....	37	23	1	61
Unknown.....	3	6	..	9
Total.....	61	55	1	117

under daily treatment with icterosan. It would appear that the use of atophan in the treatment of jaundice, as advocated by Brugsch, is not as harmless as he believed.

*Incidence.*—Since the report of the original case in 1922, an increasing number of cases has been recorded each year. We likewise have seen an increasing number of cases. The increase may be due in part to the increasing number of persons using cinchophen, and in part to the increased suspicion of the possibility of the toxicity of cinchophen. In our practice, we suspect every case of intrahepatic jaundice as being a possible case of toxic cirrhosis until the taking of cinchophen is definitely excluded. A carefully taken history and a chemical analysis of drugs when their character was not known have revealed the condition in cases which we would have missed four or five years ago.

The age of 103 patients is known. Table 1 gives the distribution by decades of life for the fatal, nonfatal and total groups. In 74 of

the 103 cases the disease occurred within the fifth, sixth and seventh decades of life, when rheumatic complaints are most frequent, and may not indicate a greater susceptibility among older persons. There were 47 men and 61 women; in 9 cases the sex was not stated (table 2).

*Symptoms.*—The initial symptoms of toxic effect are most frequently gastro-intestinal, comprising impairment of appetite, nausea and vomiting. Other symptoms are heartburn, belching and diarrhea. Pruritus, urticaria and weakness are symptoms not uncommonly encountered before the onset of jaundice, and should always warn the physician of danger in the further use of cinchophen. The mechanism of pruritus is unknown, but it resembles a similar reaction occasionally seen with hepatic injury following the use of arsphenamine. In many cases in the literature, symptoms premonitory to the jaundice are not mentioned. These symptoms may precede the jaundice by only a few days, or weeks or months may elapse before the jaundice appears.

TABLE 3.—*Incidence of Jaundice and Its Duration*

Outcome of Disease	Patients with Jaundice of Given Duration in Weeks																No. of Weeks Patients Without Jaundice	Total Number of Patients
	Number of Weeks																	
	Unknown	1	2	3	4	5	6	7	8	10	12	16	20	24	28			
Fatal.....	10	9	17	4	7	4	2	..	3	..	..	2	1	1	..	1	61	
Nonfatal.....	13	..	4	3	7	2	7	4	7	1	3	1	..	..	1	3	56	
Total.....	23	9	21	7	14	6	9	4	10	1	3	3	1	1	1	4	117	

The onset of jaundice is usually painless; however, in some instances pain is present and may be severe, although not of the grade met in biliary colic. Jaundice may be ushered in by an acute attack of nausea, vomiting, sometimes chills, fever or pain and distress in the region of the liver. The jaundice usually reaches its maximal intensity in a few days. A concentration of bilirubin of from 15 to 20 mg. in each 100 cc. of serum is observed in the moderately severe cases, and less than this in the mild cases, whereas in the fatal cases, as well as in the severe nonfatal cases, a concentration of more than 20 mg. is common, and it may attain 50 mg. for each 100 cc.

In the fatal cases, the jaundice usually remains intense until death; however, there may be a terminal fall, or death may ensue only after the disease has become chronic and the values for serum bilirubin have gradually decreased over a period of weeks. In the milder nonfatal cases, the jaundice may gradually fade from the peak. In the more prolonged and severe cases, the depth of the jaundice may remain stationary for from two to three weeks or more before fading begins. The duration in weeks of the fatal and nonfatal cases is given in table 3. The duration of the jaundice is definitely known in 50 of the 61 fatal cases. In these 50 cases, 52 per cent of the patients died within

two weeks of the appearance of jaundice, 74 per cent within four weeks and 86 per cent within six weeks. Only 8 per cent died after eight weeks. Many of the late deaths followed exploration, recurrence of jaundice or portal obstruction. The duration of the jaundice is definitely known in 40 of the 56 nonfatal cases. Recovery occurred within certain definite periods after the onset of jaundice: in 10 per cent of the cases, in two weeks; in 35 per cent, in four weeks; in 57.5 per cent, in six weeks, and in 85 per cent, in eight weeks, whereas in only 15 per cent was the duration longer than eight weeks. It would appear that most of the fatally affected patients die within six weeks, whereas those not so seriously affected recover in from six to eight weeks. The duration of the condition in nonfatal cases approximates that of the usual case of endemic "catarrhal" jaundice for which the patients seek hospitalization.

Anorexia, weakness and dehydration are often prominent features even when the jaundice is mild. Nausea may be troublesome, and pruritus is often distressing. The disappearance of the symptoms usually accompanies diminution in the depth of the jaundice, and signals the end of the hepatolysis and the beginning of recovery. In a few cases, however, the jaundice has been clearing, and weight and strength have been improving when the jaundice has recurred. Recurrences were noted in 4 cases reported in the literature, and in 2 observed by us. A fatal result ensued in 4 of the 6 cases. Some of the deaths were due to the further use of atophan. Temporary improvement should not lead to a feeling of false security and cessation of energetic treatment.

In the moderately severe nonfatal cases, headache, drowsiness and restlessness may awaken the fear that stupor and terminal coma are near. Stupor, coma, delirium and convulsions are the usual precursors of death. Seldom, if ever, does the comatose patient recover. Paralysis associated with pathologic reflexes, the presence or absence of deep reflexes and a peculiar spasticity suggestive of that seen in diseases of the extrapyramidal system and for which no gross or microscopic lesion of the central nervous system exists to explain the clinical picture may be present in the last few days. Terminal hyperpyrexia, anuria, with a rise of the value for urea in the blood, edema, anemia or a fall in the concentration of the serum bilirubin may appear.

Ascites occurred in the first three weeks of illness in only 2 cases (Cabot's case 1 and Rabinowitz' case 3), and after three weeks in 11 cases, of 117. It is usually a later, terminal phenomenon. In only 2 cases has recovery followed the appearance of ascites (Braun's case and our case 14). Paracentesis may be necessary and was reported by Link, and by Parsons and Harding. Edema may be present without

ascites (noted in 7 cases reported in the literature and in 3 of our cases), or with ascites (noted in 6 reported cases and in 3 of our cases).

Gross hemorrhage from the esophageal veins occurred as a terminal phenomenon in the cases of Willcox (case 3 in his report of 1931) and Cabot (case 1), in the fifth and sixth weeks, respectively, and was associated with ascites. Other hemorrhagic tendencies, including epistaxis, bleeding from the gums, petechiae and purpura, have been noted in fatal cases, but also in some cases in which recovery occurred.<sup>71</sup> Marked anemia was reported by Lambert, and by Parsons and Harding (case 4 in their report of 1932). Leukocytosis is occasionally noted.

In our experience, the liver was palpable and presumably enlarged in the nonfatal cases, even in the cases in which jaundice was not present. In the more severe nonfatal cases, such as our case 10, the liver was not palpated, and this was interpreted to mean a more severe degree of hepatic injury and atrophy. In most of the fatal cases, the liver could not be palpated, and at necropsy it was found to be moderately or strikingly atrophic and small. A rapid diminution in the size of an enlarged liver is of serious prognostic significance, and has been reported in several cases.

The spleen may be palpable, but is usually so only in the more prolonged cases. It has been found enlarged, as in the cases of Rabinowitz (case 1, report of 1928), Bogen (case 1) and Berger and Schweid (case 1).

In some cases diseases other than those for which the cinchophen was given were present. Thus, subacute cholecystitis without stones was present in Kingreen's case. The patient recovered after cholecystectomy had been performed. Cholelithiasis was present in Ross' second case, and the patient died following cholecystectomy. A tumor of the pituitary gland, with diabetes insipidus, was present in Hitzenberger's first case. In Singer's case, ulcerative mitral endocarditis caused death, but the jaundice was interpreted as being caused by cinchophen. Mild diabetes mellitus was present in MacGregor's case, and transient glycosuria in Ross' fourth case. In Rabinowitz' second case (report of 1930), hepatic injury and jaundice necessitated therapeutic abortion, following which the patient recovered. In Ross' third case, the patient had a tuberculous hip, operation on which was followed by death in forty-eight hours; necropsy revealed hepatic necrosis.

Various surgical procedures were carried out on other patients. Thus, abdominal exploration for abdominal pain or indefinite masses was carried out in the cases of Rake, Lowenthal, Mackay and Lowe (case 2), Bogen, Berger and Schweid and Rabinowitz (case 7, report of 1930) and the results were fatal in all. Omentopexy and gastroenterostomy were performed in Parsons and Harding's case (report of

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71. Fink.<sup>41</sup> Eimer.<sup>52</sup>

1932) with fatal results. A fatal outcome followed tonsillectomy in Rabinowitz' case 5 (report of 1930). From these results it will be seen that these patients present poor surgical risks, and that any surgical procedure should be avoided if possible.

The urine may contain albumin and tyrosine, as well as bile in appreciable quantities. The stools are clay-colored so long as the liver fails to secrete bile freely. When the liver resumes its secretory functions, bile appears freely in the duodenal drainage, the urine becomes lighter, and the stools become pigmented. The lowering of the concentration of cholesterol and cholesterol esters in the serum, as well as the abnormal output of reducing substances in the urine after the ingestion of galactose, gives valuable information regarding the degree of hepatic injury. The bromsulphalein test of hepatic function is of little value during the phase of jaundice, but is of great value in delineating the time of functional recovery of the liver after the jaundice has cleared. In our case 11, eight months had elapsed before the retention of dye disappeared.

*Diagnosis.*—The fatal cases of toxic cirrhosis caused by cinchophen are indistinguishable from the cases of acute or subacute yellow atrophy resulting from other causes. The nonfatal cases are indistinguishable from the ordinary case of catarrhal jaundice or of any other condition resulting in toxic hepatitis. Jaundice, nonobstructed bile ducts and a direct van den Bergh reaction are essential to the diagnosis of intrahepatic jaundice, whatever the cause. The diagnosis depends on a history of treatment with cinchophen. The physician will fail to elicit such a history in many cases unless every case of intrahepatic jaundice is considered to be, possibly, a case of cinchophen poisoning, and unless most careful questioning of the patient is carried out. Chemical analysis of a medium the nature of which is not known may be necessary. Suspicion that the medicine contains cinchophen, as well as appreciation of the nature of the symptoms preceding the development of jaundice, may lead to recognition of cases of toxic cirrhosis without jaundice, as in the cases of Klinkert, and in our cases 1 and 2.

Undoubtedly, some cases of idiopathic and catarrhal jaundice will, because of coincidental treatment with cinchophen, be classified as cases of toxic cirrhosis due to cinchophen. It would be much better to accuse the drug falsely than to refuse to recognize the relationship between toxic cirrhosis and cinchophen, and to permit a sensitive patient to take the drug, with recurrence of the acute process and perhaps death, as occurred in the first case reported by Reichle. The diagnosis of toxic cirrhosis due to cinchophen is unusually important because of the serious prognosis as contrasted to that of the usual case of catarrhal jaundice, and because in the nonfatal cases the patient must be pro-

tected and warned against further use of the drug. A correct diagnostic differentiation from diseases of the gallbladder or bile ducts or from portal cirrhosis is obviously important to prevent unnecessary surgical risks and postoperative deaths.

*Prognosis.*—In view of the high mortality (51 per cent) in the cases reported, the prognosis in all cases should be considered serious until the extent of the hepatic injury can be estimated. Persistent deep jaundice, a decrease in the size of the liver, mental symptoms, ascites and hemorrhagic tendencies are of particularly bad prognostic significance. The prognosis should be guarded even after recovery has set in, for there may be a recurrence. Complete clinical recovery has so far occurred in all nonfatal cases, but not enough time has elapsed since the first cases were seen for one to judge of late results. Years hence, in some of these cases, symptoms of portal obstruction, such as ascites or hemorrhage, may occur, or jaundice may again develop, leading to a fatal issue. This is, at least, to be suspected in the more severe cases.

*Treatment.*—Treatment is twofold: prophylactic and curative. Cinchophen should be administered only with due recognition of the danger to the occasional patient who may have an idiosyncrasy for the drug. It should not be given to patients who are malnourished or who have hepatic disease. The drug should be prescribed only by a physician. The use of cinchophen in patent remedies and its sale by druggists without a physician's order should be prohibited by law.

When cinchophen is to be used, it should be given intermittently. A full diet rich in carbohydrates should be a part of the treatment with cinchophen. Administration of the drug should be stopped at the first signs of toxicity, such as anorexia, nausea, weakness, vomiting, malaise, pruritus or urticaria, and treatment of the complication should be energetically pushed even before the appearance of jaundice. After the appearance of jaundice, a diet rich in carbohydrates, together with fluids, dextrose and sodium lactate intravenously, calcium lactate by mouth and duodenal drainage, has proved of value in our hands. Dextrose in the hands of some has proved more efficacious when supplemented with insulin. The use of liver extract has been advocated by Bassler, and diathermy is said to be of value.

#### SUMMARY

Although cinchophen occupies a warranted position in therapeutics, great caution is necessary in its use, as proved by the not infrequent occurrence of toxic manifestations (cutaneous, anaphylactoid, gastrointestinal, cardiac, renal or hepatic). Of these toxic manifestations, the symptoms of toxic cirrhosis are most frequently reported. Since

1923, 19 cases of toxic cirrhosis have been seen in the Mayo Clinic, and 98 cases have been recorded by various authors, 117 in all. Sixty-one of the 117 patients died. Many of the others were seriously ill, and were disabled for from one to three months. The frequency and severity of hepatic involvement establish this as the most important of the toxic manifestations.

Moreover, the frequency of the cases reported in the literature and encountered in our practice is increasing from year to year, and the 117 cases are not all the cases which have occurred. Thus, in the discussion of various cases, physicians have mentioned other unreported cases. The reports of most of the cases have come from the larger medical centers. It would be as unreasonable to assume that toxic cirrhosis caused by cinchophen occurs only in localities where larger medical centers are situated, as it would be reasonable to assume that many cases are undiagnosed or not reported. There is reason to believe that many nonfatal cases are considered to be cases of catarrhal jaundice because of lack of acquaintance with the causal relationship between cinchophen and toxic cirrhosis, with a consequent failure to seek out this cause of intrahepatic jaundice. That toxic cirrhosis without jaundice occurs and that other toxic manifestations precede, and may even accompany, hepatic injury not manifested by jaundice are even less appreciated. If all cases were recognized and reported, the number would be greater, and the problem of toxicity of cinchophen would receive greater attention.

The drug is available in a large variety of preparations; Hench has listed more than thirty. Manufacturers, recognizing the toxicity of the drug, are constantly adding new preparations, some of which are claimed to be nontoxic. It is true that toxic cirrhosis has not been reported as occurring after the use of some of these, but some preparations have so recently been placed on the market that experience with them is insufficient to allow of decision as to their toxicity. Moreover, the total quantity of cinchophen in each preparation is not known. So far, we do not feel justified in assuming that any one preparation is nontoxic.

The universal presence of the quinoline radical in all preparations points suggestively to this as the offending part of the compound. The dosage is relatively unimportant. Toxic symptoms have appeared after doses of all sizes, ranging from 54 grains (3.6 Gm.) given in five weeks to 7,200 grains (480 Gm.) given in four months. An occasional fatal case has followed the use of a very small quantity of the drug, which suggests that an idiosyncrasy was present initially, whereas in other cases the idiosyncrasy seemed to be acquired. Various theories have been evolved to explain the toxicity of the drug, but at present no satisfactory explanation exists, and experimental work has not assisted in solving the problem.



The drug has been used in a variety of conditions, chief of which are the rheumatic disorders, which are of such frequent occurrence in the later decades of life. Use of the drug has been widespread, as the drug has been readily available. Unfortunately, its use and availability have not been under the control of the medical profession. Furthermore, it has been given by some members of the medical profession without adequate knowledge of the dangers attending its use or of the significance of the premonitory symptoms. Thus, in our case 17, continuation of the administration of the drug was advised after the development of pruritus. Nor have all members of the medical profession an adequate appreciation of the seriousness of the injury caused by cinchophen, the mortality rate of which is 51 per cent, or of the risk of surgical procedures in the presence of the injury, as shown by the frequency with which the operation played a part in many of the fatalities. In view of these dangers in the use of cinchophen or allied compounds, the public should be protected by legislation or education. Members of the medical profession should be cognizant not only of the possibilities of toxic symptoms, but also of the early and mild evidences of toxicity, so that the drug may be used cautiously, its administration stopped at the first signs of poisoning, and treatment instituted even before jaundice develops.

# STUDIES ON DIGITALIS IN AMBULATORY PATIENTS WITH CARDIAC DISEASE

## V. FURTHER OBSERVATIONS ON THE NATURE OF THE CUMULATION OF DIGITALIS

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A study of the elimination of digitalis in man was published in 1929 by Gold and DeGraff.<sup>1</sup> The subjects were ambulatory patients with auricular fibrillation and moderate congestive heart failure. Slowing of the ventricular rate (depression of the auriculoventricular conduction) and the relief of the circulatory failure served as the criteria of the action of digitalis. It was found that during the first few weeks a fixed daily dose of digitalis produced progressive slowing of the ventricular rate, but that after this period the rate remained constant, although the same daily dose was continued without interruption for many weeks. A typical record obtained in the study is reproduced in chart 1. The facts were interpreted in the following manner: The progressive slowing of the ventricular rate in the first period was understood to indicate that the patient was not excreting completely each daily dose of 3 grains (0.2 Gm.), the result being cumulation of the drug, which produced a progressive increase in the intensity of the effects of the digitalis; in the second period the rate of elimination increased, the excretion keeping pace with the daily intake of 3 grains so that no further cumulation could take place. The result was that the ventricular rate reached a level at which it remained.

These explanations appeared to be the most reasonable, although the facts then available did not entirely exclude other possibilities. Since the patients being studied had auricular fibrillation and congestive failure, it seemed possible that the incomplete elimination in the early period of treatment might be due to the heart failure, and that the more

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1. Gold, H., and DeGraff, A. C.: Studies on Digitalis in Ambulatory Cardiac Patients: II. The Elimination of Digitalis in Man, *J. Clin. Investigation* 6:613 (Feb.) 1929.

complete excretion which occurred later might be ascribed to the greater capacity for elimination resulting from the improved circulation. On the other hand, it also appeared possible that the elimination of the digitalis might have remained constant throughout, the progressive slowing of the heart rate in the early period not being an indication of cumulation of the drug, but a process secondary to the improved cardiac function resulting from the continued use of a small dose of digitalis, a phenomenon which has been termed by other writers the "tonic" action of digitalis.

The general hypothesis advanced in the previous study was that patients do not excrete a fixed quantity of digitalis daily but one that varies with the amount present in the body. It would not be valid if it grew out of special conditions that apply only to patients with auricular fibrillation and congestive heart failure. The present study was planned, therefore, to ascertain the curve of the cumulation of digitalis in patients with a regular sinus rhythm without heart failure, the criteria being changes in the P R interval and in the T wave which may under these conditions be ascribed only to a direct action of the drug and which cannot be considered as indirect effects of an improved state of the general circulation.

#### METHOD

Observations were started on a series of ambulatory patients attending the clinic for cardiac diseases. Their ages ranged from 6 to 40 years. As already stated, they had regular sinus rhythms and did not present signs of congestive failure. In six, the physical signs were not sufficient to justify a diagnosis of organic heart disease (class E). The remaining patients had organic heart disease, classified etiologically as congenital, rheumatic or unknown.

A uniform specimen of digitalis was employed in the form of the compressed tablets of the dried leaf, supplied by the Heart Committee and standardized by the cat method, 100 mg. (about  $1\frac{1}{2}$  grains [about 0.1 Gm.]) constituting 1 cat unit. The drug was dispensed in the clinic, and the daily amount was ordered to be taken in a single dose before retiring.

In order to establish the normal variations in the P R intervals and in the T waves and R T segments (R T—T), several electrocardiograms to be used as controls were usually taken at intervals of a week or longer before the administration of digitalis was started, and in order to ascertain whether or not the effects observed later might have been produced by the first dose alone, the first tracing made during the administration of the drug was frequently taken from twelve to twenty-four hours after the first dose. It was found, however, that the single dose rarely produced changes; hence, in many cases the first electrocardiogram during the use of the drug was not taken until a week or more afterward. During the entire period of observations for total periods up to a year or longer, subsequent tracings were taken at intervals of from one to six weeks.

As has already been mentioned, the changes in the P R intervals and in the R T—T segments were used as criteria of the action of digitalis. The changes were read from the same lead throughout the entire experiment in any given subject, lead I or II being used depending on which was most clearly defined and could

be read with greatest precision. The standardization was recorded on each tracing. The figures for the P R intervals were not identical in different leads, and we have observed differences as high as 0.04 second. The differences, however, remained fairly constant in records taken at different times and presented no difficulty as long as readings were always made from the same lead.

In determining the degrees of change in the R T intervals and the T waves, we did not confine ourselves to the usual procedure of measuring the height of the deflections in millimeters because frequently a change in the form of the R T—T segments quite apparent to the eye was not adequately revealed in such a measurement. We found that it was more practical to compare the changes by matching the tracings according to the form of the R T—T segments or according to the actual height of the T wave in millimeters when that was possible, or according to both, and in this way we succeeded in most instances in dividing the entire series of electrocardiograms belonging to any one patient into groups according to the degree of the change. We then assigned an arbitrary value to each degree of change (each group of tracings) for purposes of charting the intensity of the effects of digitalis during different periods. The study presented an opportunity of comparing a number of electrocardiograms taken for control purposes at vary-

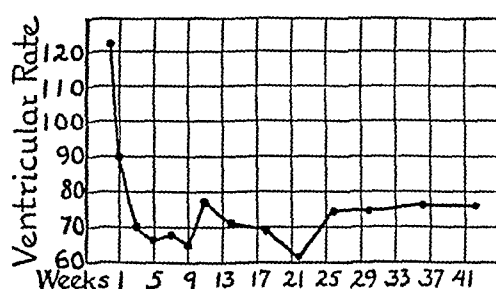


Chart 1.—The changes in the ventricular rate during the continuous administration of a daily dose of 3 grains of digitalis. The patient, E. Q., aged 25, weighed 154 pounds (70 Kg.). The diagnosis was rheumatic heart disease, mitral stenosis and insufficiency, enlargement of the heart and auricular fibrillation (class II A). When this record was started, digitalis had not been administered for three weeks.

ing intervals during periods of six months or longer. The results show that in many instances the T wave and the R T segments remain extraordinarily constant, while in others the form and the height of the T wave show similarly striking variations from time to time without any assignable reason. This is an important source of error that has not been excluded in some electrocardiographic studies found in the literature in which only one or two control records have been taken and in which a change in a patient's clinical condition or the use of some drug is assigned as the cause of the changes in the shape or the height of the T waves—changes that come well within the range of the variations that occurred spontaneously in some of our subjects.

## RESULTS

Many difficulties were encountered in the course of the experiments. It was necessary for the subjects to take a daily dose of digitalis without an interruption, or at most only an occasional one, for periods of months, and in many cases it was impossible to sustain the patient's cooperation,

especially as there were no subjective symptoms that required relief or could be relieved by digitalis. Although the subjects were urged and encouraged in every way to report all omissions of daily doses, doubt as to the accuracy of the reports in many cases made it necessary to discontinue the experiment. Intercurrent infections, intestinal upsets, vacations and inclement weather on days of sessions at the clinic (the sessions being held only once a week) often resulted in interruptions in the use of the drug for a week or more, thereby rendering valueless series of observations and tracings made during previous periods which in some cases were of several months' duration. Some patients failed to show any changes in the P R intervals or the R T—T segments of the electrocardiogram, and when changes did not appear even after many weeks or months with doses of as much as 6 grains (0.38 Gm.) daily, the experiments were discontinued. Finally, we may refer to a danger that at all times threatened to vitiate, and in some cases did vitiate, a series of observations in the large numbers of patients with rheumatic heart disease in our group, namely, periods of active carditis. The danger of this factor was particularly striking in the situation presented by two of the children with rheumatic heart disease. In one of these, after three weeks of digitalization with a daily dose of 3 grains, marked changes in the T waves and the P R intervals in lead II (an increase of from 0.15 to 0.26 second) appeared for the first time simultaneously with slight fever and pains in the joints. As the use of the drug was continued, however, the electrocardiographic changes gradually disappeared, and subsequently daily doses up to 9 grains (0.6 Gm.) failed to produce an effect on the P R intervals. In the second case, after six normal and fairly uniform control tracings were made within a period of three months, the next tracing, made on the day on which the use of digitalis was to be started, showed an inverted T wave and a prolonged P R interval. These changes progressed and then subsided spontaneously. They were proved to be due to an attack of rheumatic activity. Since there was no way of ascertaining the proper dose in every case in advance, there were many instances in which failures were recorded because the daily dose was too small to produce an appreciable effect even after months, and other instances in which the dose was so large that toxic symptoms were induced shortly after its administration was begun.

All the foregoing factors contributed their share in reducing the number of successful experiments to such an extent that on only twelve of the seventy-five subjects with whom the study was started was it possible to carry out observations that were adequate for the purpose of the investigation. The essential data obtained in these twelve patients have been summarized in the table.

*Essential Data Obtained in a Study of the Cumulation of Digitalis in Twelve Ambulatory Patients with Cardiac Disease*

Patient	Age	Weight, Pounds	Diagnosis*	Duration of Observation, Weeks†	Daily Dose, Grains	Criteria of Action of Digitalis	Effect After First Period‡	Level of Effect After Continued Administration	Duration of Level, Weeks	Effect of Larger Doses§	Size of Larger Doses, Grains
M. O.	11	86	Rheum., E. H., M. S., M. I., RSR, I	75	3	P R (0.15) R T-T, II	1+	0.21 4+	16	0.32 6+	4½
L. R.	17	180	Rheum., E. H., M. S., M. I., A. I., RSR, I	84	3	R T-T, II	0	3+	16	6+	4½
A. D.	13	80	Unknown, E. H., M. S., M. I., RSR, I	11	4½	R T-T, II	0	3+	13	6+	4½
A. R.	33	132	Rheum., E. H., M. S., M. I., A. S., A. I., RSR, IIa	75	4½	P R (0.18) R T-T, II	0.20 1+	0.22 2+	15 15	5+	6
G. W.	13	120	Rheum., E. H., M. S., M. I., RSR, I	33	3	P R (0.16) R T-T, II	0.18 2+	0.22 3+	26 26	0.28 6+	6
M. S.	15	110	Rheum., E. H., M. S., M. I., RSR, I	39	3	P R (0.20) R T-T, II	0.22 1+	0.23 5+	15 23	0.37 8+	4½ 4½
A. S.	16	113	Rheum., E. H., M. S., M. I., A. S., A. I., RSR, IIa	58	4½	R T-T, II	0	3+	9	5+	1½
E. B.	33	150	Rheum., E. H., M. S., M. I., RSR, I	50	3	R T-T, II	1+	4+	30	6+	6
H. O.	11	60	Cong., E. H., I	50	4½	R T-T, II	0	0.28 6+	8	6+	4½
G. V.	8	55	Diabetes, E	45	3	R T-T, II	0.18	0.32	11	6+	4½
N. H.	29	127	Rheum., F. H., M. S., M. I., RSR, IIa	48	4½	R T-T, II	0	4+	36	6+	6
H. J.	31	115				R T-T, II	0	6+	14	5#	

\* The diagnoses follow the nomenclature in the "Criteria for the Classification and Diagnosis of Heart Disease." Rheum., rheumatic; Cong., congenital; E. H., enlargement of the heart; M. S., mitral stenosis; M. I., mitral insufficiency; RSR, regular sinus rhythm; I, IIa, functional classification; A. S., aortic stenosis and of the action.

† This includes the period of control as well as the period after the long period of digitalization during which the drug was withheld for the study of the duration after the first one or two doses; in others, changes noted after the drug was administered for a week or longer. The intensity of the change in the R T-T segment is indicated by +, hence, for example, 5+ is a much greater change than is 1+. The changes in the P R intervals are indicated by the actual readings in seconds taken from the tracings.

‡ Under this heading are included the earliest changes observed after the drug was started. In some cases the heading refers to changes noted twenty-four hours after the first one or two doses; in others, changes noted after the drug was administered for a week or longer. The intensity of the change in the R T-T segment is indicated by +, hence, for example, 5+ is a much greater change than is 1+. The changes in the P R intervals are indicated by the actual readings in seconds taken from the tracings.

§ In cases in which the "larger doses" were not given, it was considered that the absence of gastro-intestinal or any other symptoms of the increased action of digitalis was sufficient to indicate that no appreciable cumulation was taking place during the long period marked "duration of level." In this case the dose of 4½ grains (0.3 Gm.) produced a marked change in the R T-T segment, which showed no greater change during the succeeding period in which 6 grains was administered daily for twenty-two weeks. The absence of appreciable cumulation is again indicated in this case by the absence of gastro-intestinal symptoms.

With the proper doses it was possible to demonstrate the following facts:

1. One daily dose of digitalis was insufficient to produce the full effects seen after the continued administration of the drug.
2. With the continued daily administration of digitalis a curve of increasing intensity of effects resulted.
3. After a time a level was reached beyond which the effects did not increase in intensity.
4. This level was maintained for a length of time sufficient to insure that the dose could not produce greater effects, by any criterion of the action of digitalis.
5. A larger dose was capable of producing greater effects, which indicated that the criteria employed were sufficiently sensitive to reveal the presence of more digitalis.

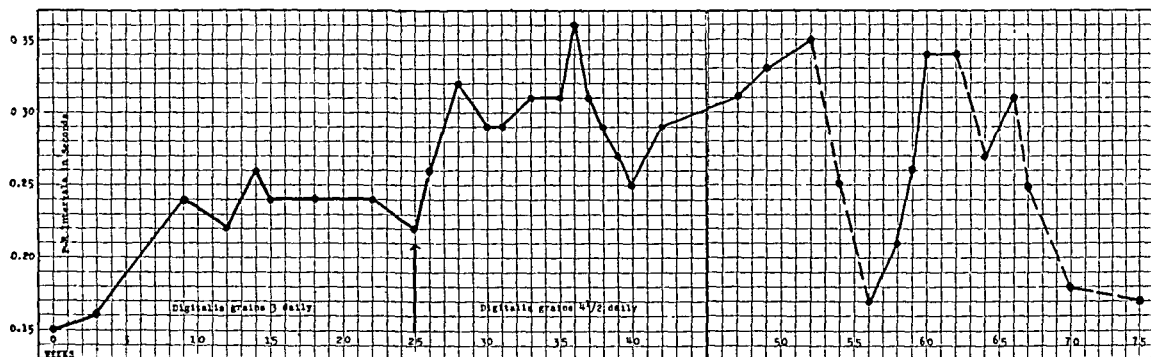


Chart 2.—The changes in the P R intervals during the continuous administration of digitalis. The arrow indicates the point at which the dose was increased from 3 to  $4\frac{1}{2}$  grains daily. The broken lines indicate the periods during which the drug was discontinued. The patient, M. C., aged 11 years, had rheumatic heart disease with enlargement of the heart, mitral stenosis and insufficiency and normal sinus rhythm (class I). There were no signs of rheumatic activity.

The details of the records of a few of the subjects have been charted and will serve to illustrate the general type of result obtained in all the others.

The observations in chart 2 were carried out in a patient, aged 11 years, over a continuous period of seventy-five weeks. For the first twenty-five weeks the patient received a daily dose of 3 grains without interruption. In the subsequent twenty-seven weeks the patient received in a similar manner a daily dose of  $4\frac{1}{2}$  grains (0.29 Gm.). An examination of this chart shows that the daily dose of 3 grains during the first period of three weeks produced practically no prolongation of the control P R interval (lead I) of 0.15 second. After this daily dose was given for a period of nine weeks the P R interval

slowly increased to 0.24 second. It remained at approximately this level during the subsequent period of sixteen weeks during which the same daily dose was taken. Since practically no effect was produced by the daily dose of 3 grains which was administered during the first three weeks, it is clear that the effects subsequently seen could not be produced by only one dose. That a marked change was evident after the dose was continued for nine weeks showed that cumulation had taken place, and that the latter change did not appreciably increase in intensity, although the same dose was continued for an additional period of nearly four months, showed that during the latter period the excretion was equal to the daily intake, and that cumulation had ceased. In order to ascertain whether further cumulation would have been revealed in the length of the P R interval had it occurred during this period, the dose was increased to  $4\frac{1}{2}$  grains daily, with the result that

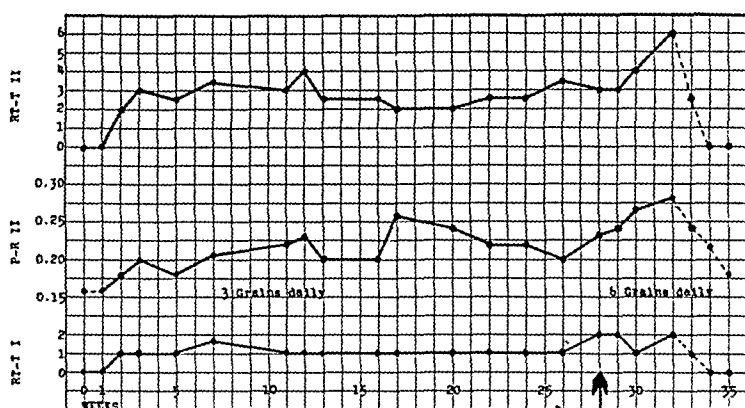


Chart 3.—The changes in the R T intervals and the T waves in leads I and II and in the P R intervals in lead II during the continuous administration of digitalis. The patient, G. W., aged 13 years, had rheumatic heart disease, enlargement of the heart, mitral stenosis and insufficiency and regular sinus rhythm (class I). The arrow indicates the day on which the daily dose of 6 grains was started. The broken lines indicate the period during which the drug was discontinued. In the case of the R T—T segment the numbers are arbitrary values assigned to indicate the intensity of the change.

the P R interval reached a much higher level (0.32 second), at which it remained with wide variations during the subsequent period of about six months during which this daily dose was continued. There were no gastro-intestinal or other symptoms during the entire period to indicate toxicity ascribable to any of the other actions of digitalis. That the effects on auriculoventricular conduction, which in this patient were ascribed to digitalis, were not due to the accident of rheumatic activity, which sometimes gives no other indication of itself than that registered in the electrocardiogram, was seen when the drug was discontinued. The result was a gradual shortening of the P R interval to practically the normal level by the fourth week. The readministration of the drug



produced essentially the same effect as before, and its withdrawal a second time again resulted in a return of the P R interval to the normal level.

The observations in chart 3 were carried out on a patient, aged 13 years, over a continuous period of thirty-five weeks. During the first period of twenty-eight weeks, a daily dose of 3 grains was taken con-

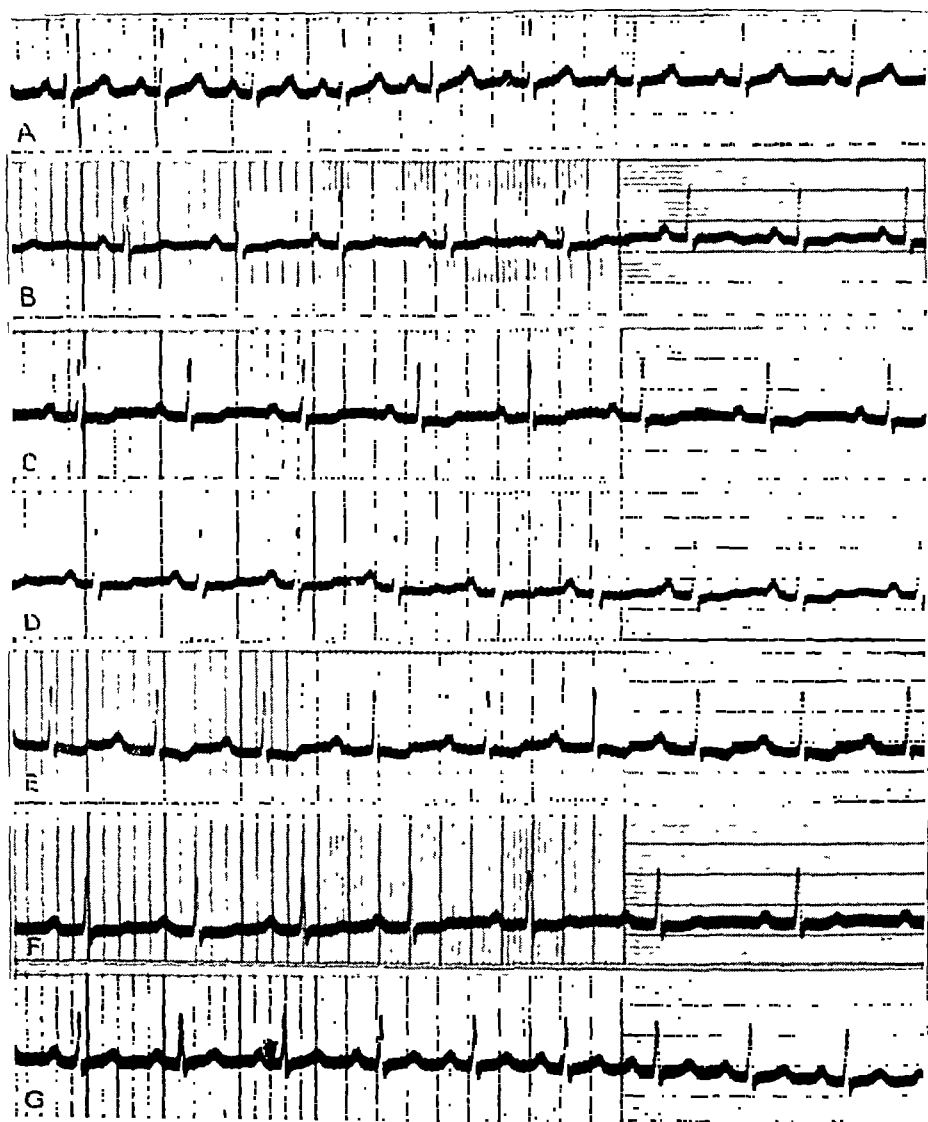


Chart 4.—Seven electrocardiograms (lead II) selected from the total series of twenty-two, which show the types of changes in R T—T to which arbitrary values have been assigned in chart 3. *A* is the control; *B*, the change after 3 grains a day had been given for one week; *C*, the slightly greater change after 3 grains a day had been given for six weeks; *D*, about the same change as in *C*, after 3 grains a day had been given for twenty-six weeks; *E*, the greater change, after 6 grains a day had been given for four weeks; *F*, partial recovery after digitalis was discontinued for one week; *G*, the change after digitalis was discontinued for three weeks.

tinuously. During the subsequent period of four weeks, a daily dose of 6 grains was taken continuously. The dose of 6 grains was not continued long enough to ascertain whether a level of effect would be obtained, the experiment being discontinued when the patient left for the country during the summer. The results obtained with the smaller dose, however, were adequate for our purpose. In this case the changes in the R T—T segment in lead II revealed the phenomenon of cumulation in the greatest detail. An essentially similar curve was obtained with the P R interval in lead II. As seen in the chart, the R T—T interval in lead I was much more resistant to changes by digitalis. Both the R T—T and the P R intervals of lead II showed during the daily dosage of 3 grains progressive increase in the intensity of the effect of digitalis, which reached a level after two weeks, remaining at that level during the subsequent period of twenty-six weeks during which the same daily dosage was given. That a greater effect on the electrocardiogram was

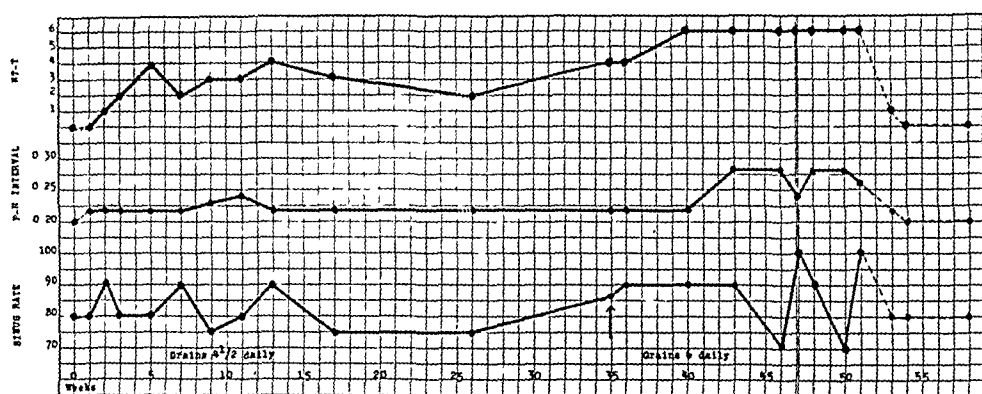


Chart 5.—The changes in the R T—T and the P R intervals and in the sinus rate during the continuous administration of digitalis. These records are taken from lead II only. The patient, E. B., aged 33, was in class E. The arrow indicates the day on which a dosage of 6 grains was started. The broken lines indicate the periods during which the drug was omitted or discontinued.

possible in this case was seen when the dose was increased to 6 grains daily.

In chart 4 are reproduced seven electrocardiograms (lead II) selected from the total of twenty-two taken during the course of the observations on this subject. They serve to show the crucial points in the study and to indicate the character of the changes to which the values in the chart are assigned.

The observations in chart 5 were carried out on a patient, aged 33, over a continuous period of fifty-eight weeks. Six selected tracings (lead II) of the total of twenty-eight made of this subject are reproduced in chart 6. During the first period of thirty-four weeks the patient received a dose of  $4\frac{1}{2}$  grains of digitalis daily,<sup>2</sup> and during the

2. In the twenty-sixth week five doses were omitted because the patient failed to return in time to obtain an adequate supply.

subsequent period of sixteen weeks she received a dose of 6 grains daily. The chart records the changes in the R T—T segment, the P R interval and the sinus rate. The curve of cumulation was studied by means of the changes in the R T—T segment, because with these progressive increase in intensity of the action of digitalis in this patient could be followed in greater detail and more satisfactorily than with any other criteria. An examination of the chart shows that after a daily dose of  $4\frac{1}{2}$

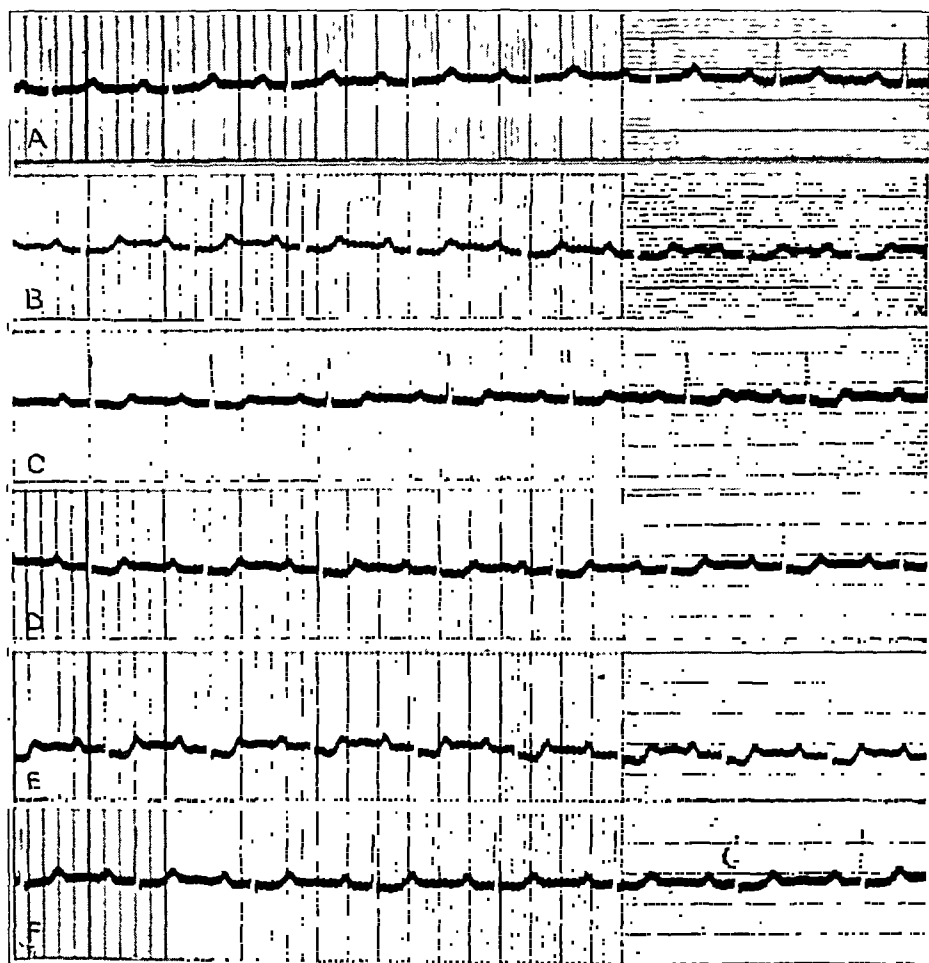


Chart 6.—Six electrocardiograms (lead II) selected from the total series of twenty-eight, which show the types of changes in R T—T to which arbitrary values have been assigned in chart 5: *A* is the control; *B*, the change after  $4\frac{1}{2}$  grains a day had been given for one week; *C*, the slightly greater change after  $4\frac{1}{2}$  grains a day for five weeks; *D*, about the same change as that in *C*, after  $4\frac{1}{2}$  grains a day for thirty-five weeks; *E*, the change after 6 grains a day; *F*, after digitalis was discontinued for two weeks.

grains for one week, there was a slight effect, i. e., lowering of the T wave, and that this change increased in intensity during the subsequent four weeks during which the same daily dose was given. Then the T wave reached a level at which it remained with variations during the sub-

sequent period of twenty-nine weeks in which this daily dose was taken. An increase in the dose to 6 grains daily resulted in a considerable increase in the intensity of the change, showing that the level during the dosage of  $4\frac{1}{2}$  grains was due to the fact that no further cumulation was taking place rather than to the failure of the index to reveal further cumulation.

The sinus rate showed marked variations throughout the course of the experiment (rates taken from the electrocardiograms), and the variations showed no relationship to the intensity of the action of digitalis. In this patient the auriculoventricular conduction showed relatively greater resistance to digitalis than did the T wave. Whereas changes in the T wave began to appear fairly promptly after the daily doses of  $4\frac{1}{2}$  grains were started, and whereas they continued to show

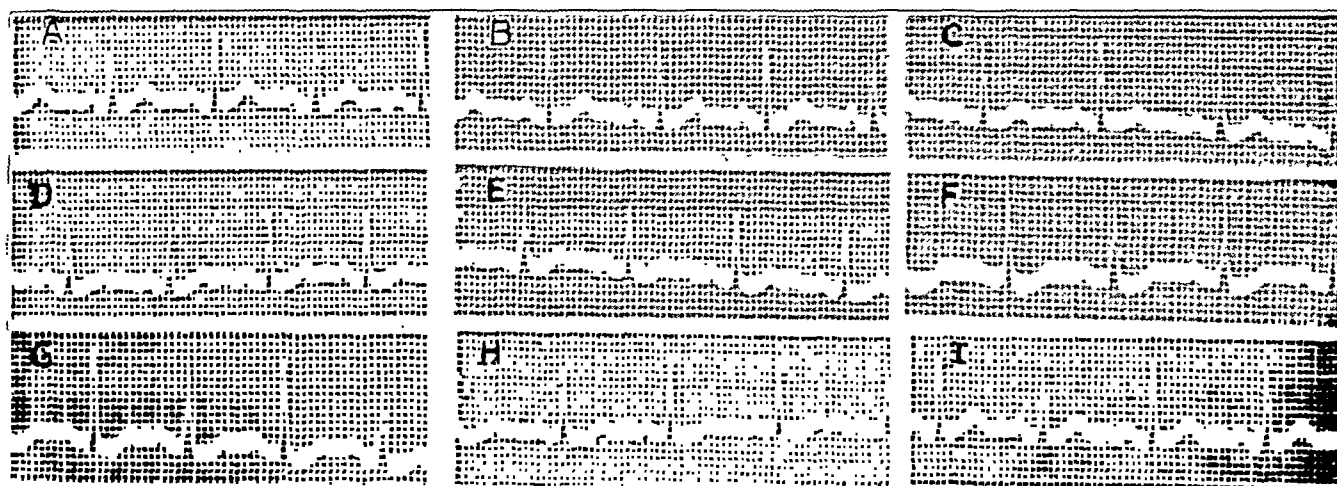


Chart 7.—Nine electrocardiograms (lead II) selected from the total of eighteen taken of patient N. H.: *A*, before digitalis was taken; *B*, no appreciable change twenty-four hours after the first dose of  $4\frac{1}{2}$  grains; *C*, slight lowering of the T wave twenty-four hours after the second dose of  $4\frac{1}{2}$  grains; *D*, a more marked change in the R T—T interval after  $4\frac{1}{2}$  grains a day had been given for one week; *E*, after  $4\frac{1}{2}$  grains a day for two weeks; *F*, after  $4\frac{1}{2}$  grains (0.3 Gm.) a day for nineteen weeks; *G*, no change greater than that in *F*, after  $4\frac{1}{2}$  grains (0.3 Gm.) a day for forty-six weeks; *H*, after digitalis was discontinued for one week; *I*, after digitalis was discontinued for two weeks.

progressive cumulation during a period of four weeks, the P R interval showed no change during this level of the action of digitalis. Marked disturbances in conduction began to appear only after the dosage of 6 grains was started. After this dosage had been continued for three weeks, loss of appetite, mild visual disturbances and depression appeared, which remained throughout the entire period in which this dosage was used, or thirteen weeks after the first appearance of these symptoms. Although marked impairment of the appetite appeared after three weeks, sufficient cumulation did not occur by the end of

thirteen additional weeks of this dosage to induce vomiting. It appears, therefore, that with the daily doses of  $4\frac{1}{2}$  grains the cumulation ceased at what might be considered a therapeutic level, whereas with the daily doses of 6 grains in this patient cumulation appears to have ceased at a minor toxic level.

In all of our experiments, when in terms of one of the criteria of the action of digitalis it appeared that cumulation had reached a level and was not increasing, an examination was made of the other effects of digitalis (other electrocardiographic changes and gastro-intestinal symptoms) to ascertain whether these might not indicate that cumulation was still taking place. The record of this patient, as well as that of the previous one, shows the need of taking into consideration more than one effect of digitalis in determining the factor of cumulation. The daily dose of 6 grains produced no prolongation of the P R interval for as long a period as five weeks, which if taken by itself would indicate that no appreciable cumulation had occurred during that time. On the other hand, the T wave showed a considerable increase in the intensity of the effect of digitalis, which would indicate that cumulation had occurred during that period.

In chart 7 are reproduced nine of a series of eighteen tracings which show in greater detail the first portion of the curve of cumulation. These were obtained in a diabetic subject (N. H.), aged 29, with a systolic murmur at the apex but no evidence of organic heart disease. As may be seen from the tracings, neither the first nor the second daily dose of  $4\frac{1}{2}$  grains produced any appreciable change in the R T—T segment. A moderate change appeared at the end of the first week, and by the end of the second week a form was established which, with moderate variations from time to time, showed no appreciable increase in the intensity of the action of digitalis, although the same daily dose was continued for a period of forty-six weeks. The absence of gastro-intestinal or any other symptoms referable to the action of digitalis indicated that after the initial period of cumulation, as shown by the R T—T changes, no further cumulation took place.

#### COMMENT

The experiments carried out in our study, therefore, confirm the conclusions of Gold and DeGraff<sup>1</sup> that patients do not excrete a fixed quantity of digitalis daily but one that varies with the amount present in the body. This is in harmony with the results of experiments with animals performed in 1912 by Hatcher<sup>3</sup> and in 1923 by Gold.<sup>4</sup> Suggestive observations in man also supporting such a view were published

3. Hatcher, R. A.: The Persistence of Action of the Digitalins, *Arch. Int. Med.* **10**:268 (Sept.) 1912.

4. Gold, H.: Digitalis Elimination, *Arch. Int. Med.* **32**:779 (Nov.) 1923.

by Bromer and Blumgart.<sup>5</sup> This view signifies, by way of illustration, that a patient who has received 300 minims (18.48 cc.) of tincture of digitalis in twenty-four hours will excrete more during the following day than one who has received only 50 minims (3.08 cc.). Although the statement may appear self-evident to some, it is at variance with the quite prevalent view that patients excrete about from 20 to 30 minims (1.2 to 1.8 cc.) of the tincture daily regardless of the quantity above these doses that is given.<sup>6</sup>

The practical importance of a clear differentiation of the two views lies in the fact that both are employed as a basis for statements regarding the dosage of digitalis which are mutually contrary. Those holding the latter view maintain that it is irrational to attempt to digitalize patients from the start with daily doses of the size of the so-called excretion doses, because such quantities are in themselves too small to produce the full effects, and because their continued use would fail to result in cumulation. With the premise being a fixed quantity of excretion daily, this conclusion seems reasonable. It is, however, contrary to the experience of many who have found that some patients can be satisfactorily digitalized by the continued use of daily doses as small as 30 minims of the tincture. The former view, which is supported by this study, is, on the other hand, in harmony with this experience, as well as with the results of the work of Gold and DeGraff<sup>7</sup> on the dosage of digitalis which show that the full therapeutic effects can be induced in the average ambulatory patient, although it takes longer, by the daily administration of quantities as small as from 3 to 4 grains (from 0.2 to 0.26 Gm.) of the drug, and that this dosage can then be continued for many months as the daily maintenance dosage without the occurrence of toxic symptoms. The explanation of this experience is that the patient who can eliminate 30 minims of the tincture daily after some of the drug has accumulated is unable to eliminate that dose daily at the start. In more general terms, this signifies that the cumulation of digitalis is a self-limiting process. As we have already shown, this fact can be demonstrated in only a restricted range of dosages. If the doses are too small, cumulation will cease at a level which fails to cause perceptible effects. If the doses are too large, toxic symptoms may be produced before a level is reached.

5. Bromer, A. W., and Blumgart, H. L.: The Maintenance Dose of Digitalis, *J. A. M. A.* **92**:204 (Jan. 19) 1929.

6. Pardee, H. E. B.: The Continued Use of Digitalis, *New York State J. Med.* **22**: 131 (March) 1922.

7. Gold, H., and DeGraff, A. C.: Studies on Digitalis in Ambulatory Cardiac Patients. IV. Newer Principles of Digitalis Dosage, *J. A. M. A.* **95**: 1237 (Oct. 25) 1930.

It should be emphasized that the observations made in this study are to serve to explain the successful use of small doses in digitalization and to point out the cause of some contradictions found in the literature. This is not intended as a plea for the use of small doses as a routine, particularly for patients with advanced congestive heart failure for whom there can be no question that more rapid digitalization by the use of larger doses at first and smaller doses subsequently for maintaining effects is the more desirable procedure.

# EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

## II. RELATIONSHIP OF LEFT VENTRICULAR HYPERTROPHY, THE WIDTH OF THE CARDIAC MUSCLE FIBER AND HYPERTENSION IN THE RAT

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It has long been recognized that hypertension is commonly accompanied by enlargement of the left ventricle. The cause for cardiac hypertrophy has been studied in recent years and the condition appears to be due solely to hypertrophy of the individual fibers rather than to hyperplasia. If this is correct, it would seem that some direct relationship between the height of the blood pressure, the degree of left ventricular enlargement and the width of the muscle fiber should exist. However, there has been surprisingly little study to establish such a relationship. To date the number of observations is insufficient to permit the application of statistical methods to this problem.

Pässler and Heinecke,<sup>1</sup> in their classic study of the relationship between cardiac hypertrophy and hypertension in partially nephrectomized dogs, employed the ratio of the weight of the left ventricle to the weight of the right ventricle as an index of hypertrophy of the left side. By this method they found that hypertrophy of the left ventricle accompanied hypertension, but their method of separation of the ventricles for weighing was obscure. They did not measure the individual cardiac muscle fibers.

The outstanding contribution to the subject of the rôle of the cardiac muscle fibers in cardiac hypertrophy and atrophy in man was made by Karsner, Saphir and Todd.<sup>2</sup> They selected one normal, one hypertrophied and one atrophic human heart for microscopic study and

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From the Laboratory of Physiological Chemistry of the University of Virginia.

1. Pässler and Heinecke: *Versuche zur Pathologie des Morbus brightii*, *Verhandl. d. deutsch. path. Gesellsch.* 9:99, 1905.

2. Karsner, H. T.; Saphir, Otto, and Todd, T. W.: *Cardiac Muscle in Hypertrophy and Atrophy*, *Am. J. Path.* 1:351 (July) 1925.



measurement. The hypertrophied heart was obtained from a patient who died of chronic nephritis. It was found that cardiac hypertrophy was due principally to enlargement of the fibers without hyperplasia, and that the fibers in the hypertrophied heart were appreciably wider, on the average, than those in the normal heart. A sufficient number of fibers was measured to permit statistical analysis. Atrophy was likewise shown to be due partially to a reduction in the size of the fibers. Since only one hypertrophied heart was studied, it was obviously impossible to show that the enlargement of the fibers was proportional to the hypertension or to the cardiac enlargement.

By assuming that an increase in the width of the fibers is an indication of cardiac hypertrophy, Mark and Geisendörfer<sup>3</sup> demonstrated cardiac hypertrophy in five partially nephrectomized dogs. The readings of the blood pressure in these animals were above normal. Since only a small number of observations was available, no conclusive relationship between the blood pressure and the width of the fibers could be deduced. These workers expressed the opinion that hypertrophy began in the left ventricle and eventually involved the right ventricle, but the evidence which they offered for this conception is not convincing.

A recent interesting observation on the width of fibers has been made by Harrison, Ashman and Larson.<sup>4</sup> They compared the pulse rate with the width of the fibers in several species of normal animals and found the slower heart rates associated with relatively thick fibers and, conversely, the faster rates with relatively thin fibers. The rat had the fastest rate and the thinnest fibers of all the species investigated.

During the last few years a series of experiments on partially nephrectomized rats has been conducted in this laboratory.<sup>5</sup> Hypertension, cardiac and renal hypertrophy, retention of nitrogen and polyuria were produced in these animals. In the experimental animals it was shown that there was a high statistical correlation between the height of the blood pressure and the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio. It should be pointed out that the hypertension was dependent on one factor, namely, an experimentally produced renal insufficiency. The possi-

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3. Mark, R. E., and Geisendörfer, H.: Untersuchungen über die Nierenfunktion: Zur Frage des Zusammenhanges von Nierenmasse, Herzhypertrophie und Blutdrucksteigerung, *Ztschr. f. d. ges. exper. Med.* **74**:350, 1930.

4. Harrison, T. R.; Ashman, R., and Larson, R. M.: Congestive Heart Failure: XII. The Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart, *Arch. Int. Med.* **49**:151 (Jan.) 1932.

5. Chanutin, Alfred, and Ferris, E. B., Jr.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: I. Control Diet, *Arch. Int. Med.* **49**:767 (May) 1932.

bility of an additional correlation between the blood pressure, the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the width of the fibers suggested itself. Accordingly, additional partially nephrectomized animals were studied in sufficient numbers to permit statistical analysis.

## METHODS

The cardiac tissue was chosen at random from experimental animals. These animals were subjected to two-stage operations during which approximately 80 per cent of the total tissue of the kidney was removed. Animals which represented graded blood pressures were selected for study. Unilaterally nephrectomized and intact laparotomized animals were included in this series. All animals were mature and in good condition when they were killed. A variety of diets (table 1) was fed to the experimental rats.

TABLE 1.—Diets Fed Experimental Animals

Diet	Whole Liver, Gm.	Dried Ex-tracted Liver, Gm.	Dried Ex-tracted Beef, Gm.	Liver Extract, Ce.*	Lard, Gm.	Cod Liver Oil, Gm.	Starch, Gm.	Yeast, Gm.	Salt Mixture, Gm.	Cholesterol, Gm.	Uric Acid, Gm.	Sodium Bicarbonate, Gm.
1	20	..	..	..	14	5	52	5	4	..	..	..
2	40	..	..	..	16	5	30	5	4	..	..	..
3	60	..	..	..	14	5	12	5	4	..	..	..
4	80	..	..	..	6	5	..	5	4	..	..	..
5	..	80	..	..	6	5	..	5	4	..	..	..
6	..	..	80	..	10	4	..	6	4	..	..	..
7	..	..	20	30	..	5	37	4	4	..	..	..
8	10	..	..	..	14	5	62	5	4	..	..	..
9	15	..	..	..	18	5	53	5	4	..	..	..
10	..	..	20	..	16	5	50	5	4	..	..	..
11	..	..	20	..	14	5	47	5	4	..	5	..
12	..	..	20	..	10	5	44	5	4	..	..	10
13	..	..	20	..	13	5	50.5	5	4	2.5	..	..

\* 30 cc. is equivalent to a concentrated extract of 225 Gm. of raw liver.

The method of obtaining the blood pressures has been described in a previous paper.<sup>5</sup> The carotid artery was cannulated in the rat anesthetized with ether, and the final reading was taken while there was a corneal reflex, but before there was any struggling.

For histologic study the hearts were fixed in Zenker's fluid to which solution of formaldehyde had been added, embedded in paraffin and sectioned at 6 microns. Some hearts were sectioned longitudinally so as to include only the left ventricle. In others, small portions were cut at different angles and levels so as to include both the right and the left ventricle. No effort was made to study any particular section of the right or the left ventricle, since the width of the fibers at different levels seemed uniform.

An attempt was made to measure the width of the longitudinally cut fibers at the nucleus with a filar micrometer, but this procedure was found extremely difficult. Accordingly, a more convenient method for measuring the width of the fibers was designed. The microscope was tilted to a horizontal position, and a powerful Leitz microscope lamp was used as a source of illumination. The section to be studied was held in a mechanical stage and the image thrown on a screen 18 inches (45.72 cm.) from the eyepiece of the microscope. A high, dry lens was used. The field was magnified 740 times by this arrangement. This was done in a dark room. Satisfactory fields for study were easily found. The widths

of the projected fibers were measured in centimeters with accurate calipers. Duplication was carefully avoided. These measurements were readily transposed into microns. Every fiber which had its nucleus well centered and its edges well outlined was measured.

In this series the weight of the heart represents the right and left ventricles after the atria were removed. It is realized that absolutely accurate weights of the remaining ventricles could not be obtained because of the difficulty in removing the atria.

In the statistical analysis of the measurements, standard formulas for standard deviation, correlation coefficient and probable error were used.

## RESULTS

The pertinent data are presented in table 2. They are arranged in the order of increasing blood pressures (first column). The third, fourth and fifth columns show, respectively, the average widths of the fibers, representative standard deviations and the numbers of fibers counted in the left ventricles. Corresponding data for the right ventricles are given in the sixth, seventh and eighth columns. Because of the consistency of the figures obtained for the right ventricle, no effort was made to study all the hearts. The method of sectioning the right ventricle permitted a relatively small number of counts to be made, but the uniform average figures and their standard deviations seem to indicate a good index of reliability.

An analysis by standard deviations of the measurements of the fibers of the left ventricle of a control animal (rat 535) indicated that 68 per cent of all readings lay between 13.34 and 15.66 microns. On the other hand, fibers from a hypertrophied heart (rat 650) showed a variation between 19.20 and 25.42 microns. Comparison of the frequency distribution<sup>6</sup> for the control and the hypertrophic hearts showed significant differences, which are illustrated in table 3. The majority of the measurements of the widths of the individual fibers of the left ventricles of the control hearts fall within a very narrow range (from 0.85 to 1.30 cm.). This is in contrast to the wide range of frequency (from 1 to 2.30 cm.) seen in the hypertrophic hearts. An interesting observation which should be emphasized is that the fibers of the right ventricle are consistently smaller and fall within a narrower range of frequency than those of the left ventricle, regardless of the blood pressure; in other words, the fibers of the right ventricle in hypertension are narrower than the normal fibers of the left ventricle (tables 2 and 3). Karsner and his associates<sup>2</sup> also noted the greater frequency distribution in the hypertrophic heart. This may be due, in part, to the

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6. Frequency distribution refers to the total frequency of the fibers included in each step-interval (0.05 cm.). For example, for the left ventricle of rat 535, twelve fibers are included in the step-interval from 0.95 to 1 cm., or from 12.84 to 13.51 microns.



Fig. 1 (rat 677).—Section of the left ventricle, showing the typically normal width of the fibers under an oil immersion lens;  $\times 900$ .



Fig 2 (rat 622) —Section of the left ventricle, showing the typically enlarged width of the fibers under an oil immersion lens;  $\times 900$ .

TABLE 2.—Results of Experimentation

Systolic Blood Pressure, Mm.	Heart Weight $\times 100$ Surface Area	Left Ventricle			Right Ventricle			Rat	Weight, Gm.	Duration of Experiment, Days	Age at Death, Days	Diet (Table 1)	Procedure*
		Width of Fiber, Microns	Standard Deviation	Fibers Counted	Width of Fiber, Microns	Standard Deviation	Fibers Counted						
106	0.187	15.3	....	50	12.5	1.33	27	87	192	112	398	10	C (2)
110	0.176	16.4	....	54	11.8	....	24	335	259	4	335	10	C (2)
112	0.166	14.3	1.96	50	12.0	0.91	27	20	192	133	334	10	C (2)
116	0.202	16.2	....	70	12.5	1.92	37	75	255	140	256	10	C (2)
116	0.185	14.4	....	60	12.7	1.48	22	543	252	97	337	10	C (2)
118	0.205	14.2	....	60	12.9	....	39	135	302	207	246	10	C (2)
118	0.203	15.7	1.64	84	....	....	..	648	160	68	141	10	C (2)
120	0.192	14.6	....	44	....	....	..	311	212	12	241	10	C (2)
120	0.178	14.5	....	57	....	....	..	23	160	136	327	10	C (2)
122	0.190	15.2	....	76	....	....	..	615	306	104	176	2	C (2)
124	0.179	15.1	....	30	....	....	..	106	208	174	223	10	Op
124	0.161	14.9	1.62	74	....	....	..	659	144	95	156	5	Op
126	0.172	15.3	....	70	11.8	1.11	27	19	225	133	326	10	Op
126	0.222	18.2	....	46	....	....	..	601	233	42	207	10	Op
126	0.174	15.5	....	79	....	....	..	677	256	47	122	2	Op
130	0.199	15.3	....	89	....	....	..	653	217	68	137	1	C (2)
130	0.175	15.3	1.60	83	....	....	..	655	260	68	129	4	C (1)
132	0.180	14.9	1.62	87	....	....	..	577	197	107	182	4	C (2)
132	0.203	14.9	....	95	....	....	..	606	295	148	216	2	Op
134	0.208	19.7	....	63	14.0	....	32	587	329	37	274	10	Op
136	0.200	17.0	....	64	12.2	....	20	35	366	213	520	10	C (2)
136	0.163	14.5	1.16	70	....	....	..	535	177	133	190	6	C (2)
138	0.183	16.0	....	61	12.7	....	27	14	286	167	234	10	C (2)
138	0.192	17.5	1.89	101	....	....	..	553	303	113	182	4	C (2)
138	0.182	14.7	....	105	....	....	..	690	207	47	123	3	C (1)
140	0.187	20.3	....	69	12.7	....	31	175	301	99	153	10	C (2)
142	0.197	18.4	....	33	....	....	..	593	149	40	120	10	Op
142	0.165	15.0	1.62	90	....	....	..	522	203	140	196	12	Op
142	0.187	15.6	....	99	....	....	..	589	267	69	136	3	Op
144	0.196	17.3	2.02	72	....	....	..	521	273	140	196	12	Op
145	0.183	14.2	....	50	....	....	..	90	188	79	289	10	C (2)
146	0.197	17.8	1.55	87	....	....	..	656	274	68	129	4	Op
146	0.199	17.5	....	95	....	....	..	599	235	107	181	3	Op
147	0.202	18.3	....	39	....	....	..	432	98	10	154	10	Op
148	0.191	20.5	....	64	....	....	..	1231	180	98	174	11	Op
150	0.215	20.0	....	78	12.9	....	30	585	299	37	274	10	Op
150	0.165	17.7	1.62	49	....	....	..	594	162	139	203	3	Op
152	0.218	20.5	2.43	26	....	....	..	879	222	28	100	7	Op
153	0.204	17.4	1.62	84	....	....	..	524	344	140	196	12	C (2)
154	0.270	19.3	....	60	....	....	..	370	208	72	195	10	Op
156	0.287	20.7	....	58	12.5	1.42	25	478	228	91	246	10	Op
158	0.226	19.2	1.81	45	....	....	..	450	188	164	201	7	Op
160	0.201	20.0	2.50	107	....	....	..	691	248	47	117	4	C (1)
160	0.233	19.6	....	24	....	....	..	1326	122	160	229	9	Op
162	0.257	20.7	2.48	70	....	....	..	786	128	241	305	8	Op
164	0.217	21.2	2.68	33	....	....	..	336	265	176	220	7	Op
164	0.250	19.5	....	58	....	....	..	484	212	177	235	12	Op
164	0.184	19.6	....	97	....	....	..	676	215	47	122	2	Op
166	0.256	20.9	....	73	14.7	....	26	918	246	226	296	1	Op
166	0.219	21.2	2.39	36	14.6	....	25	928	248	210	289	13	Op
168	0.267	20.2	....	50	14.5	....	30	785	132	241	305	8	Op
170	0.264	20.4	....	86	....	....	..	534	200	133	190	6	Op
170	0.258	19.4	....	66	12.8	1.51	26	552	278	96	244	10	Op
172	0.247	19.3	....	75	12.5	....	24	425	292	43	267	10	Op
172	0.234	19.3	....	31	....	....	..	576	174	90	260	10	Op
174	0.238	19.3	2.57	55	12.5	1.18	23	59	144	121	201	10	Op
174	0.203	20.5	....	88	....	....	..	679	157	47	122	2	Op
176	0.221	20.2	1.38	31	....	....	..	633	214	196	281	1	Op
178	0.261	21.6	....	60	12.7	1.42	15	479	262	109	269	10	Op
178	0.264	18.8	2.03	39	....	....	..	714	212	92	162	2	Op
180	0.258	21.4	....	60	11.8	....	17	465	328	113	320	10	Op
180	0.213	20.7	....	38	....	....	..	504	245	112	191	10	Op
184	0.296	22.6	....	73	11.3	1.47	24	439	338	133	272	10	Op
186	0.254	19.2	....	50	....	....	..	532	256	123	231	10	Op
187	0.205	20.8	....	54	12.4	....	26	455	362	105	333	10	Op
188	0.211	20.1	....	74	....	....	..	407	247	182	226	1	Op
190	0.308	19.8	....	59	....	....	..	97	158	200	415	10	Op
190	0.229	21.6	1.96	49	....	....	..	449	185	164	201	7	Op
192	0.244	22.4	....	50	12.4	0.95	22	433	303	122	257	10	Op
194	0.248	21.9	2.72	81	....	....	..	622	227	72	134	4	Op
194	0.208	22.0	2.25	35	15.0	....	..	700	....	....	....	10	Op
196	0.238	20.8	....	40	....	....	..	466	356	116	355	10	Op
198	0.212	18.9	....	43	....	....	..	500	....	....	....	10	Op
198	0.242	21.7	2.41	26	....	....	..	600	....	....	....	10	Op
200	0.265	22.2	....	47	12.7	1.51	30	505	188	115	192	10	Op
200	0.242	22.3	3.12	121	....	....	..	650	189	68	137	1	Op
212	0.281	21.9	2.24	45	....	....	..	539	293	87	150	2	Op
214	0.248	22.2	....	47	....	....	..	166	248	170	238	10	Op
230	0.310	23.6	4.45	64	....	....	..	163	207	225	293	10	Op

\* C (1) indicates unilateral nephrectomy; C (2), both kidneys intact; Op, approximately 80 per cent of total kidney tissue removed.

difficulty of obtaining sections through or sufficiently close to the center of the nucleus of the large fibers, as well as to the unquestionable difference in the size of the individual fibers.

Early in this study it was suggested that there might be a quantitative relationship between the breadth of the fibers of the left ventricle and the blood pressure. In many cases a preliminary glance at several fields of a section allowed the observer to approximate the blood pressure

TABLE 3.—*Frequency Distribution of the Width of the Fibers*

Width of Fibers (Arbitrary Units)		Number of Fibers			
Centimeters (Magnification × 740)	Microns	Left Ventricle		Right Ventricle	
		Control	Hypertrophic Heart	Control	Hypertrophic Heart
0.65	8.78	0	0	1	0
0.70	9.47	0	0	1	0
0.75	10.15	0	0	5	3
0.80	10.80	0	0	5	0
0.85	11.49	1	0	3	9
0.90	12.19	1	0	7	8
0.95	12.84	12	0	5	3
1.00	13.51	13	1	3	4
1.05	14.18	15	0	2	1
1.10	14.87	12	0	2	0
1.15	15.56	9	2	1	1
1.20	16.23	5	1	1	0
1.25	16.90	2	3	1	0
1.30	17.56	0	7	0	1
1.35	18.24	0	5	0	0
1.40	18.92	0	6	0	0
1.45	19.60	0	8	0	0
1.50	20.23	0	9	0	0
1.55	20.95	0	10	0	0
1.60	21.60	0	11	0	0
1.65	22.33	0	8	0	0
1.70	22.92	0	9	0	0
1.75	23.60	0	7	0	0
1.80	24.30	0	9	0	0
1.85	24.98	0	7	0	0
1.90	25.68	0	4	0	0
1.95	26.35	0	5	0	0
2.00	27.02	0	3	0	0
2.05	27.70	0	2	0	0
2.10	28.40	0	1	0	0
2.15	29.10	0	1	0	0
2.20	29.70	0	0	0	0
2.25	30.40	0	1	0	0
2.30	31.09	0	0	0	0
		Rat 535	Rat 650	Rat 75	Rat 505

of the animal with surprising accuracy. An examination of figures 1 and 2 shows the typical differences seen in a control and in a hypertrophic heart. A statistical analysis of the data for the blood pressure and the width of the fibers of the left ventricle gave a correlation coefficient and probable error of  $0.795 \pm 0.027$ . These figures denote a "high relationship" between the two factors studied. The individual data are plotted in figure 3.

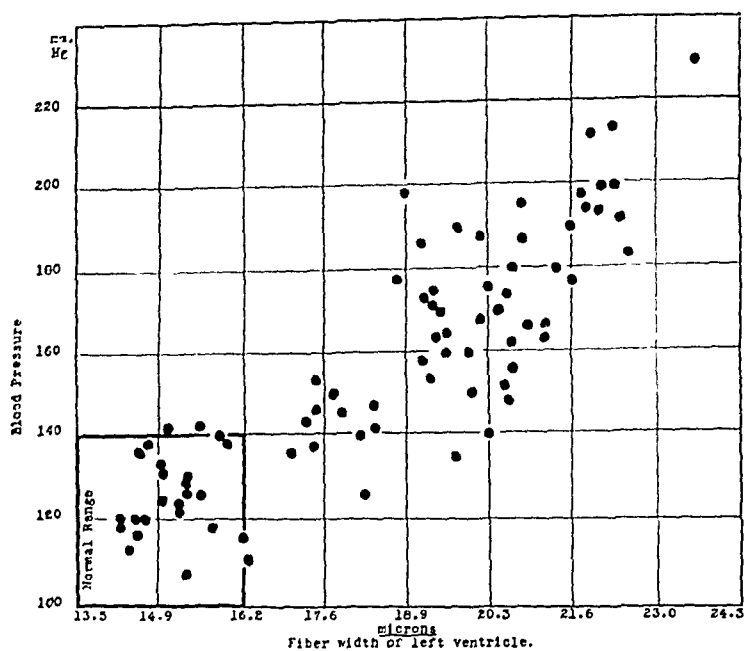


Fig. 3.—High relationship between the blood pressure and the width of the fibers of the left ventricle.

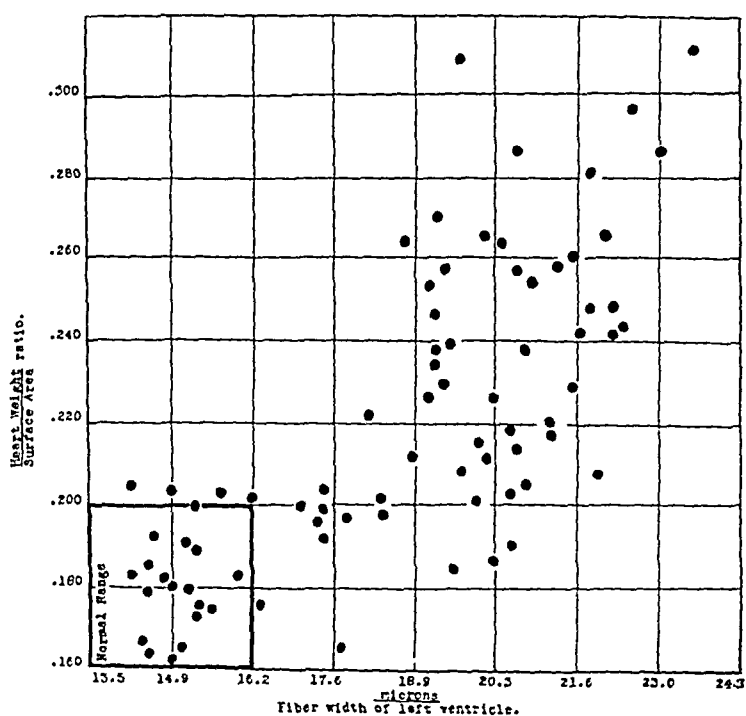


Fig. 4.—Substantial or marked relationship between the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the width of the fibers of the left ventricle.



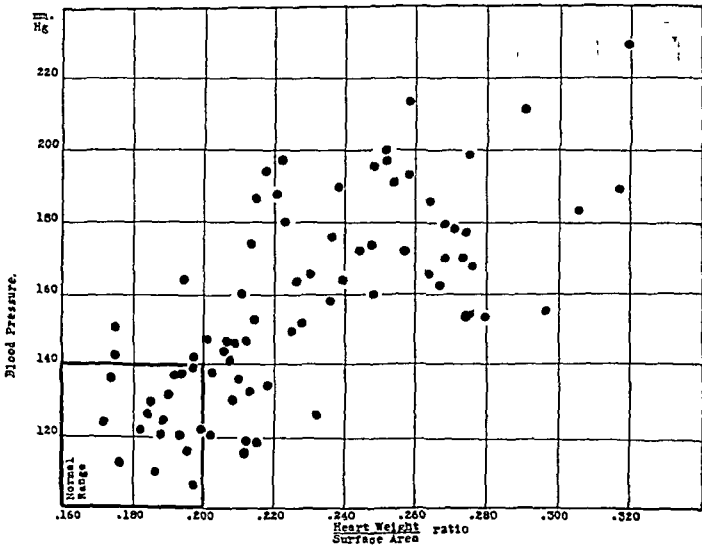


Fig. 5.—Relationship between the blood pressure and the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio.

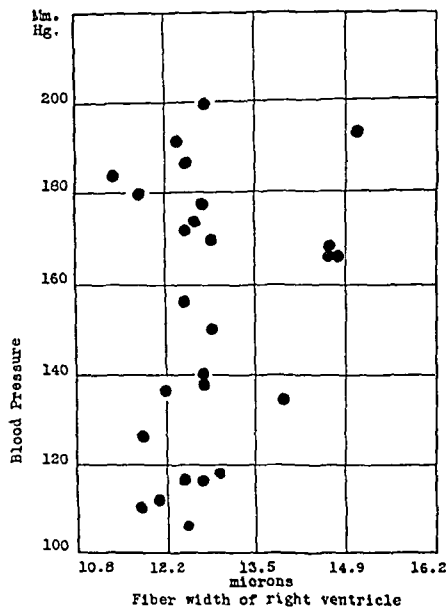


Fig. 6.—Lack of correlation between the blood pressure and the width of the fibers of the right ventricle.

Since it is common practice among pathologists to use the weight of the heart as an indication of hypertrophy, the correlation coefficient and its probable error for the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the width of the fibers of the left ventricle were calculated and found to be  $0.690 \pm 0.039$ . These figures represent the upper limits of a "substantial or marked relationship." The detailed data are presented in figure 4.

In a previous paper,<sup>5</sup> a high positive relationship (correlation coefficient and probable error =  $0.86 \pm 0.028$ ) was shown to exist between the blood pressure and the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio. By using additional measurements to study this relationship, the correlation coefficient of

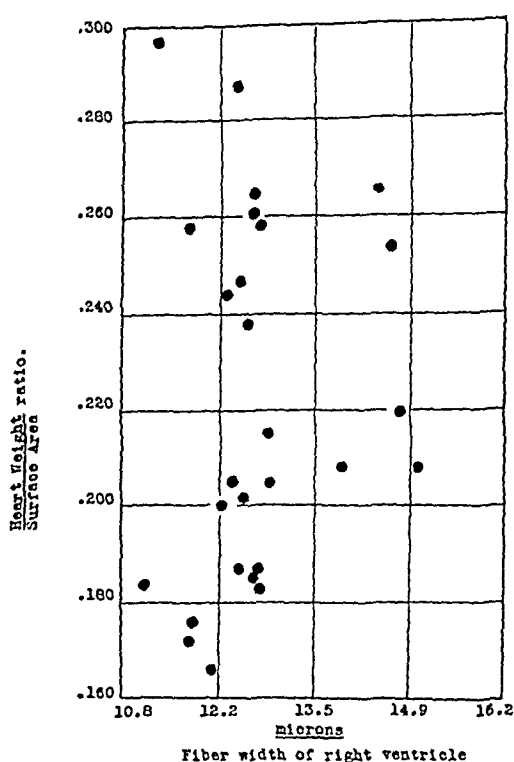


Fig. 7.—Lack of correlation between the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the width of the fibers of the right ventricle.

$0.75 \pm 0.027$  was obtained. Although these figures have been lowered, they are still within the range of a very high relationship. A detailed presentation of these measurements is given in figure 5.

A study of the measurements shown in figure 6 demonstrates a total lack of correlation between the blood pressure and the width of the fibers of the right ventricle. The same fact holds true for the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the width of the fibers of the right ventricle (fig. 7).

#### COMMENTS

The objections that may be raised against the procedure used for obtaining the systolic blood pressures in our rats are: (1) the use of an

anesthetic, (2) the operation that is necessary for isolating the carotid and (3) the inability to obtain more than one reading of the blood pressure. It is believed that the statistical analyses given justify this method of obtaining the blood pressures. Furthermore, the assumption is reasonable that the blood pressure remains constant within a very narrow range of fluctuation during any given period. It is also apparent that the relationships pointed out between the blood pressure, the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the width of the fibers are independent of the time necessary for the development of the various stages of hypertension and cardiac hypertrophy.

There are several observations that may be of importance in determining cardiac hypertrophy in man and in the experimental animal at autopsy. The weight of the heart may or may not be an accurate index of hypertrophy, since the size of the organ is dependent to a great extent on the weight or the surface area of the animal. For example, two rats used as controls, weighing 170 and 340 Gm., had hearts weighing 0.495 and 0.760 Gm., respectively, but the  $\frac{\text{heart weight}}{\text{surface area}}$  ratios were the same. With high blood pressure the smaller rat may have a heart the weight of which may approach that of the heart of a larger control animal. From these observations it seems logical to assume that the weight of the heart should be related to some unit such as the body weight or the surface area.

Since there is a marked degree of constancy in the width of the fibers of the left ventricle of the control rat, and since hypertension is accompanied by a positive deviation from the control values, it is suggested that similar studies be applied to other species. Karsner and his associates<sup>2</sup> emphasized the increased width of the cardiac fibers as a criterion for the demonstration of cardiac hypertrophy in human beings. An approach to the problem of recognizing cardiac hypertrophy should be feasible through a study of the width of the cardiac fibers.

#### SUMMARY

A series of seventy-nine experimental rats in which the blood pressures varied from 106 to 230 mm. of mercury was studied in an effort to correlate the blood pressure, the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the width of the fiber of the left and the right ventricles.

A statistical analysis of the results demonstrated the following facts:

1. A high relationship between the blood pressure and the width of the fibers of the left ventricle (correlation coefficient and probable error =  $0.795 \pm 0.027$ ).

2. A substantial relationship between the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the width of the fibers of the left ventricle (correlation coefficient and probable error =  $0.690 \pm 0.039$ ).

3. A high relationship between the blood pressure and the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio (correlation coefficient and probable error =  $0.750 \pm 0.027$ ).

4. A total lack of correlation between the width of the fibers of the right ventricle and the blood pressure or the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio.

In the control animals, the average width of the fibers of the right ventricle was less than that of the fibers of the left ventricle. There was no increase in the width of the fibers of the right ventricle in the hypertrophied hearts.

# ELECTROCARDIOGRAPHIC STUDY OF CORONARY OCCLUSION

FURTHER OBSERVATIONS ON THE USE OF CHEST LEADS

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When acute coronary occlusion is produced in the dog, the conventional limb leads often yield an inadequate record of the change which takes place in the action current of the heart. However, when electrodes are applied in certain positions on the wall of the chest, clearly significant electrical disturbances can be recorded which may be partly or completely missed in the tracings of the limb leads.<sup>1</sup> The electrocardiograms obtained from limb leads and chest leads supplement one another. If both are used together, a much more complete electrocardiographic picture of the effects of experimental coronary occlusion can be obtained.

These results in the dog suggested the use of chest leads in the study of acute coronary occlusion in man.<sup>2</sup> It was found that a similar situation presented itself: Chest leads yielded information that could not be obtained from limb leads. Moreover, it became evident that in certain cases this information was essential for correct electrocardiographic diagnosis. Since these observations were first made, thirty-six

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1. Wood, F. C., and Wolferth, C. C.: An Electrocardiographic Study of Coronary Occlusion: The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Currents, *J. Clin. Investigation* **11**:815 (July) 1932; Experimental Coronary Occlusion: Inadequacy of the Three Conventional Leads for Recording Characteristic Action Current Changes in Certain Sections of the Myocardium; an Electrocardiographic Study, *Arch Int. Med.* **51**:771 (May) 1933.

2. (a) Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* **183**:30 (Jan.) 1932; (b) Further Observations upon the Use of Chest Leads in the Electrocardiographic Study of Coronary Occlusion, *M. Clin. North America* **16**:161 (July) 1932.

cases<sup>3</sup> of acute coronary occlusion have been studied with chest leads as well as with limb leads. Six have come to necropsy. The present paper consists of a discussion of the findings in these cases.

#### METHOD AND MATERIAL

*Type of Electrodes.*—Our early tracings<sup>2a</sup> were made by applying the ordinary large wrap electrodes of German silver to the chest, over pads moistened in warm salt solution. The use of copper disk electrodes 3.5 cm. in diameter and 1 cm. in thickness is less cumbersome, and is the method of choice at present. These electrodes are applied over small pads of absorbent cotton moistened in salt solution. They are held in position by adhesive tape, or by a light band of some resilient material encircling half the chest. It is essential that skin resistance be low enough to avoid distortion of the tracings. This can be effected by rubbing the skin with alcohol and by firm application of electrodes.

*Leads Used.*—The majority of the cases reported in this paper have been studied with three chest leads in addition to the conventional limb leads. The electrodes were applied as follows: The right arm electrode was placed on the anterior surface of the chest; the left arm electrode was placed on the posterior surface; the left leg electrode occupied its usual position on the left lower extremity. The exact positions are described in the next paragraph. For convenience, the anteroposterior lead is referred to as lead IV, as was done in a previous publication;<sup>2a</sup> the anterior-left leg lead is termed lead V, and the posterior-left leg lead is called lead VI. Further discussion of the relative usefulness of these three chest leads will be undertaken elsewhere in the paper.

*Variations in the Tracing Obtained by Varying the Locations of the Electrodes.*—Chart 1 *A* illustrates the electrocardiograms which were obtained for a normal person from electrodes situated at various designated points. When small electrodes are used, a relatively small change in the position of the anterior electrode may cause considerable alteration in the tracing. On the other hand, the posterior electrode can be moved in a comparable way without causing any definite change in the electrocardiogram.<sup>4</sup> In our studies, the posterior electrode has been placed at a point just below and mesial to the left scapular angle, with the arm at the side. The anterior electrode has been placed in two different positions: (1) at the apex of the heart and (2) at a point

3. These cases were obtained from the wards of the University of Pennsylvania Hospital, the Philadelphia General Hospital, the Mount Sinai Hospital and the Pennsylvania Hospital and from private practice.

4. This point has not been tested in a series of pathologic cases. It is possible that a large heart or a posterior infarct might give different results. However, in one case of probable posterior infarct, moving the posterior electrode produced no definite effect except to cause minor variations in lead VI.

4 cm. to the left of the sternum, in the fifth interspace. The latter point has been the one most frequently used in the past, but the apical position is probably the better of the two for studying most cases of coronary occlusion. The only difference in the tracings for the normal person is that when the electrode is placed at the apex the initial downward deflection of Q R S in leads IV and V is deeper and the upward deflection which follows may be smaller. In pathologic cases, however, especially in cases of presumable posterior infarction, the deviations of the RS-T interval which appear in leads IV and V may be slightly larger when the anterior electrode is over the apex. Care must be taken not to allow the anterior electrode to be displaced upward, to the right or too far beyond the apex to the left. Marked variations in the character of the tracing can occur if this source of error is not foreseen and prevented. In this connection it might be mentioned that the large electrodes used in the early stages of this study <sup>2a</sup> seem to be less subject to error. Small changes in position do not seem to cause marked alterations in the electrocardiogram. Moreover, the tracings are comparable to those obtained with small electrodes at or near the apex, although the Q R S complexes and T waves may be slightly smaller.

*Normal Controls.*—Chart 1 B illustrates the appearance of six leads for a normal person. A series of thirty normal persons has been studied. In leads IV and V, the P wave is often small, diphasic or inverted. The Q R S complex consists of a large initial downward deflection, usually followed by an upward deflection. The RS-T interval is often quite short, giving way rapidly to the deeply inverted T wave. In the tracings of all normal persons in which there has been no deviation of the RS-T interval in the limb leads, this interval has begun on the iso-electric line or within 1 mm. below it. Slight depressions of RS-T must be interpreted with caution; slight elevations of this interval are probably more significant. The T wave is definitely inverted for all our normal persons and is usually of considerable magnitude. The characteristics of lead VI and its normal variations seem to be similar to those of lead III.

*Abnormal Variations in the Absence of Definite Cardiac Infarction.*—Thus far, leads IV and V have shown the following variations: The initial downward deflection of Q R S may be absent in the tracings of certain patients with marked right axis deviation, of some persons with left bundle branch block (new nomenclature) and of some with evidence of myocardial disease without a definite history of coronary occlusion. This deflection may be small for some persons with left bundle branch block or for patients with lesser degrees of right axis deviation. The T wave has been upright for certain patients with myocardial disease. The RS-T interval is readily depressed below the iso-electric line as an artefact due to "overshooting." True deviations

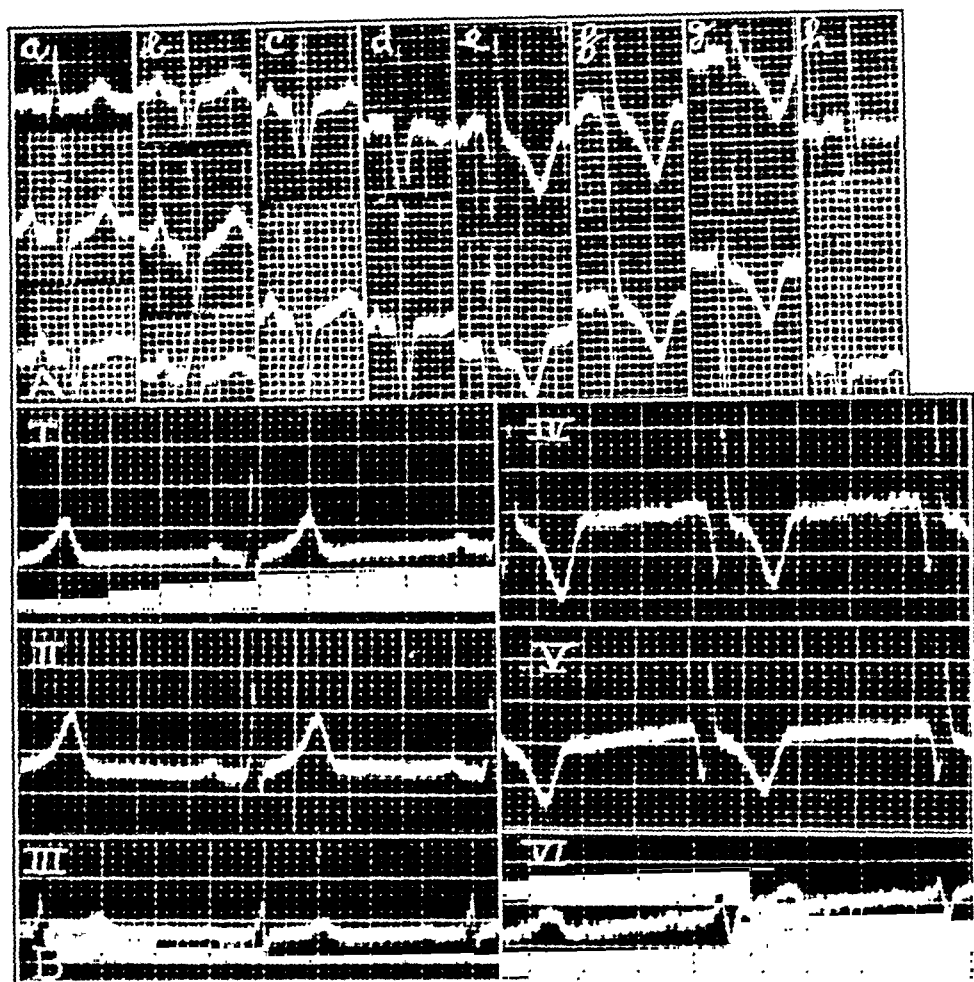


Chart 1.—*A*, electrocardiograms of a normal youth, aged 21, obtained by varying the position of the anterior electrode on the chest. For the sake of brevity, any anteroposterior lead is called lead IV. Lead V is any lead from the anterior surface of the chest to the left leg. Lead VI is the lead from the posterior surface of the chest to the left leg. *a*, indicates three limb leads; *b*, leads IV, V and VI—anterior electrode at the aortic area; *c*, leads IV and V—anterior electrode at the pulmonic area; *d*, leads IV and V—anterior electrode in the third left interspace, 4 cm. from the sternum; *e*, leads IV and V—anterior electrode in the fourth left interspace, 4 cm. from the sternum; *f*, leads IV and V—anterior electrode in the fifth left interspace, 4 cm. from the sternum; *g*, leads IV and V—anterior electrode just to the left of the apex pulse; *h*, leads IV and V—anterior electrode in the fourth right interspace, 2 cm. from the sternum.

At about the level of the fourth rib the tracing in this patient changes abruptly. The initial downward deflection of Q R S becomes more prominent; the terminal downward deflection disappears, and the T wave becomes deeply inverted.

*B*, six leads in a normal youth, aged 20. The anterior chest electrode was 2 cm. inside the apex impulse. The posterior chest electrode was just inside the angle of the left scapula. The initial downward deflection of Q R S in leads IV and V is prominent. It is followed by an upward deflection. The RS-T interval is short and begins at least 1 mm. below the iso-electric line. Therefore, small depressions of RS-T in leads IV and V when unassociated with other findings must not be stressed as diagnostically significant. Small elevations in RS-T may be more important. The T waves in leads IV and V are deeply inverted. Lead VI is somewhat like lead III with a deeper S wave.



of the RS-T interval are to be expected in all those conditions which produce them in the limb leads,<sup>5</sup> but are not always present in these conditions. They are therefore probably no more nor less pathognomonic of recent cardiac infarction than are similar deviations in the three conventional leads. In the absence of acute infarction, we have seen such deviations in leads IV and V of persons with acute rheumatic myocarditis, of persons with left bundle branch block and of certain patients with presumably damaged hearts who were given digitalis.<sup>6</sup> The dose of digitalis required to produce them seems to be smaller in old than in young persons. One patient, aged 78, showed a depression of the RS-T interval in lead IV after taking 32 cc. of the tincture in eight days. In this case, however, the persistence of the initial downward deflection helped to differentiate the condition from the cases of cardiac infarction to be described later.

The abnormal variations in lead VI are similar to those seen in lead III.

#### CASES OF CARDIAC INFARCTION WITH ELECTROCARDIOGRAPHIC STUDY AND NECROPSY

CASE 3.—M. C., a white woman, aged 52, had been known to have a systolic blood pressure of about 200 mm. of mercury for at least four years. One year before admission she suffered an attack suggestive of coronary occlusion, and made a fairly satisfactory recovery. On March 16, 1932, she was again seized with a severe pain over the heart, associated with a reduction of blood pressure to 150 systolic and 100 diastolic. On March 17 she was admitted to the medical wards of the Philadelphia General Hospital, where a clinical diagnosis of acute coronary occlusion was made. She became progressively worse and died on March 26.

The electrocardiograms of this patient are shown in chart 2. There was nothing strikingly significant of recent cardiac infarction in the three limb leads in any one tracing, although on March 22 lead I showed a suggestion of elevation of the RS-T interval. Leads IV and V showed a marked depression of the RS-T interval throughout and an absence of the initial downward deflection of Q R S. The Q waves and inverted T waves in leads II, III and VI suggested the presence of an old posterior infarct.

Necropsy was performed by Dr. B. A. Gouley. The heart showed hypertrophy and considerable generalized coronary sclerosis. There was an old occlusion of the posterior descending branch of the right coronary artery, with an organized infarct and beginning cardiac aneurysm. This lesion involved the lower part of the posterior surface of the left ventricle, the posterior portion of the apex of the heart and the adjacent posterior section of the interventricular septum. A recent occlusion of the left anterior descending coronary artery was found, 1 cm. beyond its origin. An acute infarct was located in the distribution of this artery. It involved the anterior surface of the left ventricle, including the apex and the anterior part of the interventricular septum. It extended around the lateral surface

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5. Wolferth, C. C.: *Diseases of the Heart and Blood Vessels*, in *Progressive Medicine*, Philadelphia, Lea & Febiger, 1931, vol. 3, p. 169.

6. Bellet and McMillan: Unpublished observations.

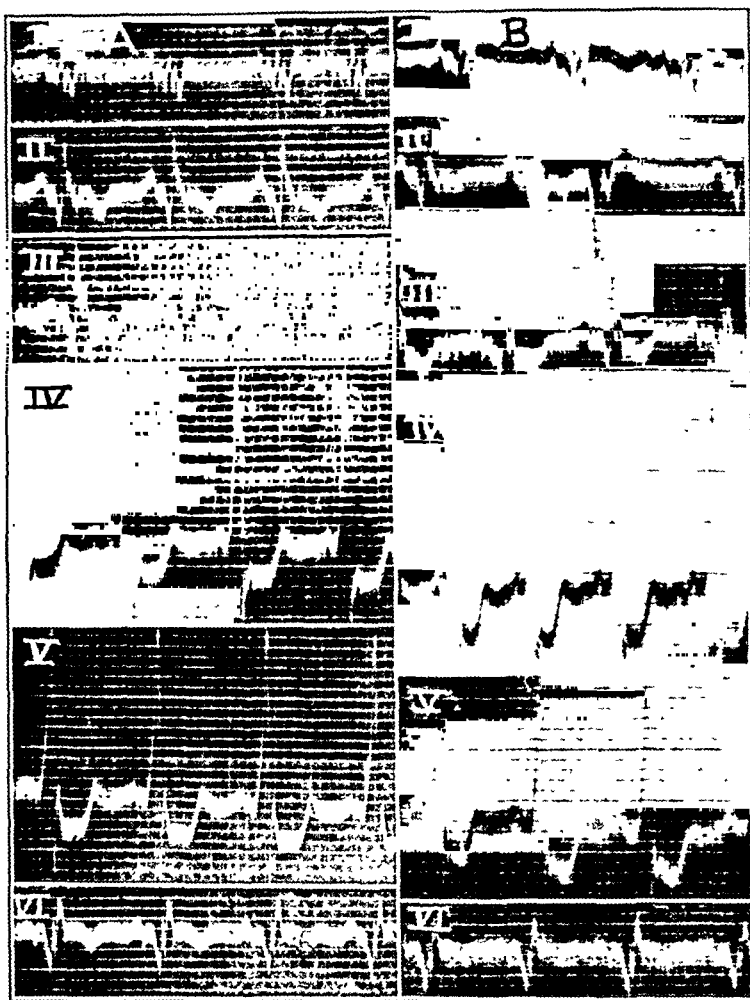


Chart 2.—Electrocardiograms of case 3, an example of group A. The anterior electrode was placed at the apex beat. Acute coronary occlusion occurred on March 16, 1932. *A*, six leads taken March 21, five days later. No definite changes of the RS-T interval are present in the limb leads. Depressions of the RS-T interval of 3 mm. are seen in leads IV and V. The initial downward deflection of Q R S in leads IV and V is absent. The occurrence of a Q wave and an inverted T wave in leads II, III and VI suggests the presence of a previous posterior infarct. At necropsy, an old posterior and a recent anterior infarction were found in the left ventricle.

*B*, six leads, taken March 23, seven days after the attack. A small elevation of the RS-T interval has appeared in lead I. The RS-T interval in lead III shows a suggestion of depression. In other respects, the tracing is much the same as the previous one. Leads IV and V show an absence of the initial downward deflection of Q R S and a 4 mm. depression of the RS-T interval.

of the heart, owing to obstruction of all the lateral branches of the anterior descending artery. A mural thrombus was adherent to the inner surface of the recent infarct. A rupture 2 cm. in length was found at about the middle of the lesion.

*Summary.*—A patient with an old posterior and recent anterior infarction presented an electrocardiogram with suggestive elevation of the RS-T interval in lead I, a definite depression of the RS-T interval in leads IV and V and an absent initial downward deflection in leads IV and V.

CASE 4.—D. G., a white man, aged 42, was admitted to the Mount Sinai Hospital on Oct. 23, 1932, in a state of collapse. The day before admission while he was apparently well, he was seized with a severe pain over the heart. The pain continued. He became weak and vomited several times. On admission he was described as obese, pallid, dyspneic and cyanotic. The skin was moist. The cardiac rate was 140 per minute; the rhythm was regular. The blood pressure was 80 systolic and 70 diastolic. There were râles at each base. A diagnosis of acute coronary occlusion was made. The patient died on October 26.

An electrocardiogram was taken on October 25 (chart 3A). The RS-T interval was elevated in lead I and markedly depressed in leads IV and V. A Q wave was present in lead I. The initial downward deflection in leads IV and V was considerably diminished in size but was present.

Necropsy was performed by Dr. D. Meranze on October 26. The heart was moderately enlarged, weighing 500 Gm. There was an acute occlusion of the left anterior descending coronary artery, beginning just below the point of origin of the circumflex branch. An acute infarct involved the entire anterior surface of the left ventricle, the apex, the lateral wall, the anterior part of the interventricular septum and the lower fourth of the posterior wall. The pericardium over this lesion showed inflammatory changes. Mural thrombi were present in the left ventricle. The other coronary arteries were atheromatous but patent. An interesting anomaly in this patient was that the posterior wall of the left ventricle was supplied by the circumflex branch of the left coronary artery, not by the right coronary artery.

*Summary.*—The patient had acute occlusion of the left anterior descending coronary artery. An electrocardiogram taken on the third day showed an elevation of the RS-T interval in lead I and a marked depression of this interval in leads IV and V.

CASE 5.—A. L., a white man, aged 55, was known to have had hypertension for five years. On May 28, 1932, he suffered a severe attack of pain over the heart. The pain subsided the next day, but his condition became progressively worse. He was admitted to the Philadelphia General Hospital seven days later (June 4) moribund. Dyspnea, cyanosis, low blood pressure (90 mm. of mercury systolic), cold moist skin, pulmonary congestion and tachycardia (130 per minute) were the striking features. He died on June 5.

An electrocardiogram was taken on June 4, seven days after the onset (chart 3B). Lead I showed the suggestion of an elevation of the RS-T interval. Leads IV and V showed slight depressions of this interval, but these depressions were much smaller than those usually seen in anterior infarction. There was no Q wave in leads II and III to suggest the presence of a previous posterior infarction.

Necropsy was performed by Dr. R. P. Custer. There was an old infarct in the lower half of the posterior wall of the left ventricle. A recent occlusion of the left anterior descending coronary artery was found 1.5 cm. from its origin. The

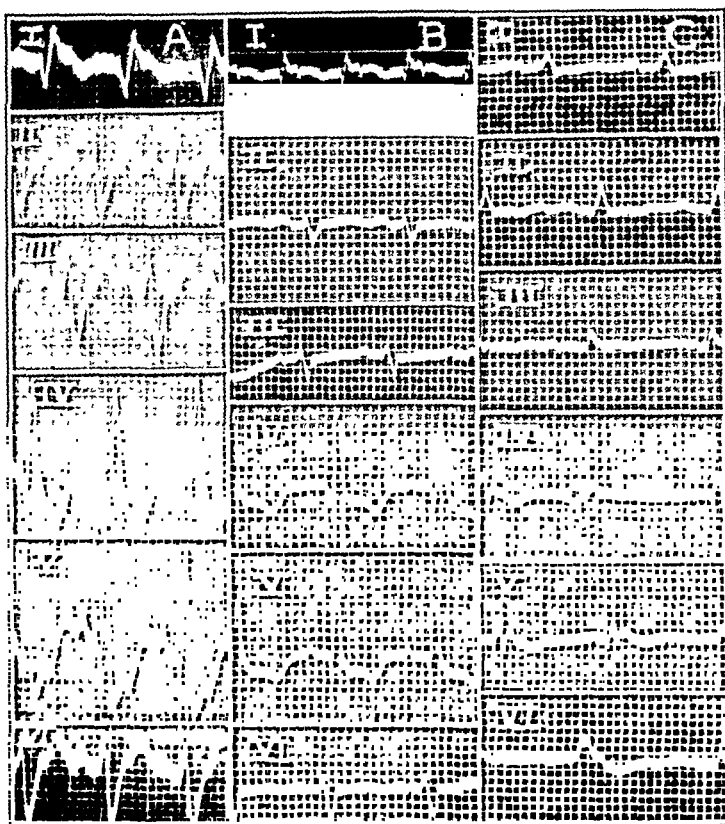


Chart 3.—*A*, electrocardiograms of case 4 taken Oct. 25, 1932, with the anterior electrode over the apex impulse. Acute coronary occlusion occurred October 22. The Q R S complexes are all widened and slurred. Lead I shows a Q wave and an elevation of the RS-T interval. Leads II and III show no changes in the RS-T interval. Leads IV and V show small initial downward deflections of Q R S and depressions of the RS-T interval. Lead VI resembles lead III. At necropsy, a recent infarction of the anterior surface of the left ventricle was found. This is an example of a case in group A.

*B*, electrocardiograms of case 5 taken on June 4, 1932, with the anterior electrode over the apex impulse. Acute coronary occlusion had taken place on May 28, one week previously. Lead I shows an RS-T interval elevation. Leads II and III show nonspecific findings. The Q R S complexes are small. In leads IV and V the initial downward deflection of Q R S is small. There is only a slight depression of the RS-T interval. Lead VI resembles lead III. At necropsy, an acute infarction of the anterior surface of the left ventricle was found.

*C*, electrocardiograms of case 34 taken on June 12. Acute coronary occlusion probably occurred on June 7, five days previously. All the Q R S complexes and T waves are small. No findings suggestive of acute coronary occlusion were noted. At necropsy, extensive old infarction was present in both the anterior and the posterior walls of the left ventricle. A small recent infarct, 2 cm. in diameter was found at the extreme apex of the heart.

acute infarction involved the lower two thirds of the anterior surface of the left ventricle, the apex and the anterior half of the interventricular septum. The recent thrombosis had not involved the main left lateral branches of the anterior descending coronary artery; consequently the infarct did not extend around the left lateral border of the heart.

*Summary.*—A patient with acute coronary occlusion showed only slight deviations of the RS-T interval in any of the six leads seven days after the onset. At necropsy, an old posterior and a recent anterior infarct were found.

CASE 34.—J. S., a white man, aged 67, had suffered with dyspnea on exertion for more than a year. On June 7, 1932, he was suddenly seized with a severe pain in the epigastrium and the left hypochondrium, and became markedly short of breath. He was admitted to the Philadelphia General Hospital on June 12, acutely ill with urgent dyspnea, feeble heart sounds, a cardiac rate of 109 per minute and a blood pressure of 90 systolic and 70 diastolic. Congestion was present in the liver and the bases of the lungs. The patient became progressively worse and died on June 16.

Electrocardiograms were taken six, seven and eight days after the onset (chart 3 C). The complexes were all of extremely low amplitude. No characteristic deviation of RS-T were seen in any of the tracings.

Necropsy was performed by Dr. R. P. Custer. The heart showed extensive coronary sclerosis. An old occlusion of the right coronary artery was found 3 cm. from its origin. The entire posterior wall of the left ventricle was the seat of an old infarction. There was also an old occlusion of the left anterior descending artery with infarction of the anterior wall of the left ventricle and the formation of an aneurysm in its lower half. A small recent infarction, 2 cm. in diameter, was found at the extreme apex. Its surface presented downward toward the diaphragm. A mural thrombus was attached to its inner surface. The ventricular wall at this point was only 2 mm. thick. A large clot was found in the lower end of the aorta at its bifurcation. (The pain in the upper part of the abdomen was attributed to coronary occlusion rather than to the aortic thrombus.)

*Summary.*—A patient with extensive coronary sclerosis and with old infarcts in both the anterior and the posterior surfaces of the left ventricle suffered a small infarction at the extreme apex. Six days later there was no deviation of the RS-T interval in any lead. The electrocardiographic complexes were small and bizarre, and yielded no diagnostic information concerning the recent infarct.

CASE 19.—W. M. B., a white man, aged 54, was well until Oct. 16, 1932. On that day he experienced an attack of substernal pain radiating to both arms, lasting four hours. This was diagnosed coronary occlusion by his physician; the patient was kept in bed continuously from that time on. He had a brief attack of substernal discomfort on October 17. Then he remained free from pain until December 22. That evening about midnight he had another severe seizure lasting about four hours. He was admitted to the medical wards of the Hospital of the University of Pennsylvania on December 24, in the service of Dr. Alfred Stengel. He was apparently comfortable. The blood pressure was 160 systolic and 100 diastolic. The aortic second sound was accentuated. The heart was moderately enlarged. There were no evidences of congestive heart failure. The tentative diagnosis was: occlusion of several relatively small coronary arteries, coincident with the previous attacks of pain. At 4 a. m. on December 28, another attack began. This was more severe than any previous one, and lasted fourteen hours despite the repeated administration of morphine. There was a rise of temperature the next day. The leukocyte count was 14,000. The blood pressure dropped to

140 systolic and 110 diastolic. The pulse rate, which had been about 80 per minute, rose gradually to 110 per minute. A diagnosis of another coronary occlusion was made. Death occurred on December 30, at 5 a. m., during an attack of cardiac pain.

The electrocardiograms of this patient are shown in chart 4. The first tracing (December 24) showed no deviation of the RS-T interval. The findings were those of an old anterior infarct. The large T waves in leads IV and V suggested a possible small recent occlusion superimposed on the old one. The second electrocardiogram (December 27) showed no deviation of the RS-T interval, but the change which had taken place in the contour of the tracing in three days made us feel more certain that a recent small infarction had occurred. The third (December 28) and fourth (December 29) electrocardiograms showed unmistakable evidence that the attack on December 28 had been due to a large infarction in the anterior surface of the left ventricle.

Necropsy was performed by Dr. Parsons on December 30. The heart showed moderate enlargement. The posterior surface of the left ventricle was normal, and the arteries in that region were relatively free from sclerosis. There was marked sclerosis of the arteries on the anterior surface of the left ventricle. There was a recent red thrombus obstructing the left anterior descending coronary artery, 1.5 cm. from its origin. There was acute infarction of the lower two thirds of the anterior surface of the left ventricle. The left ventricular wall just above and mesial to the apex was thinned out and showed a slight bulge. This point was the seat of old infarction. In addition, one of the small lateral branches of the left anterior descending artery was obstructed by an organizing thrombus. The exact order of events could not be determined at necropsy. Nevertheless it was evident that a recent acute occlusion of the main left anterior descending coronary artery had taken place (probably on December 28), and that at least two smaller occlusions had previously occurred in the distribution of this artery.

*Summary.*—This patient probably suffered several attacks of coronary occlusion before coming to the hospital. An electrocardiogram on admission showed the findings of an old anterior infarction and certain indications that a small recent occlusion had taken place. On December 28, while the patient was in the hospital, another attack occurred. An electrocardiogram on that day showed an elevation of the RS-T interval in lead I and a depression in leads II and III. Leads IV and V showed an absence of the initial downward deflection of Q R S and a deep depression of the RS-T interval. Necropsy showed a recent occlusion of the main left anterior descending coronary artery and at least two small infarcts of less recent origin in the distribution of this artery.

CASE 33.—H. R., a white man, aged 61, gave a history of an attack suggesting coronary occlusion in 1927. He then remained well until 11 a. m. on Jan. 4, 1933, when he was seized with intense pain in both arms extending from the shoulders to the finger-tips. He also had slight pain across the chest at the level of the clavicles. He was admitted to the medical wards of the Pennsylvania Hospital in the service of Dr. Arthur Newlin on January 4. On admission he was prostrated, sweating and weak. The pulse rate was 90 per minute. The blood pressure was 180 systolic and 130 diastolic. The liver was enlarged and tender. There were râles at the bases of both lungs. The next day, fever and leukocytosis were present, and the blood pressure dropped to 100 systolic and 75 diastolic.

The electrocardiographic studies are shown in chart 5. Leads II and III showed deep Q waves and elevations of the RS-T interval. Lead IV showed an absence of the initial downward deflection of Q R S and a slight elevation of the

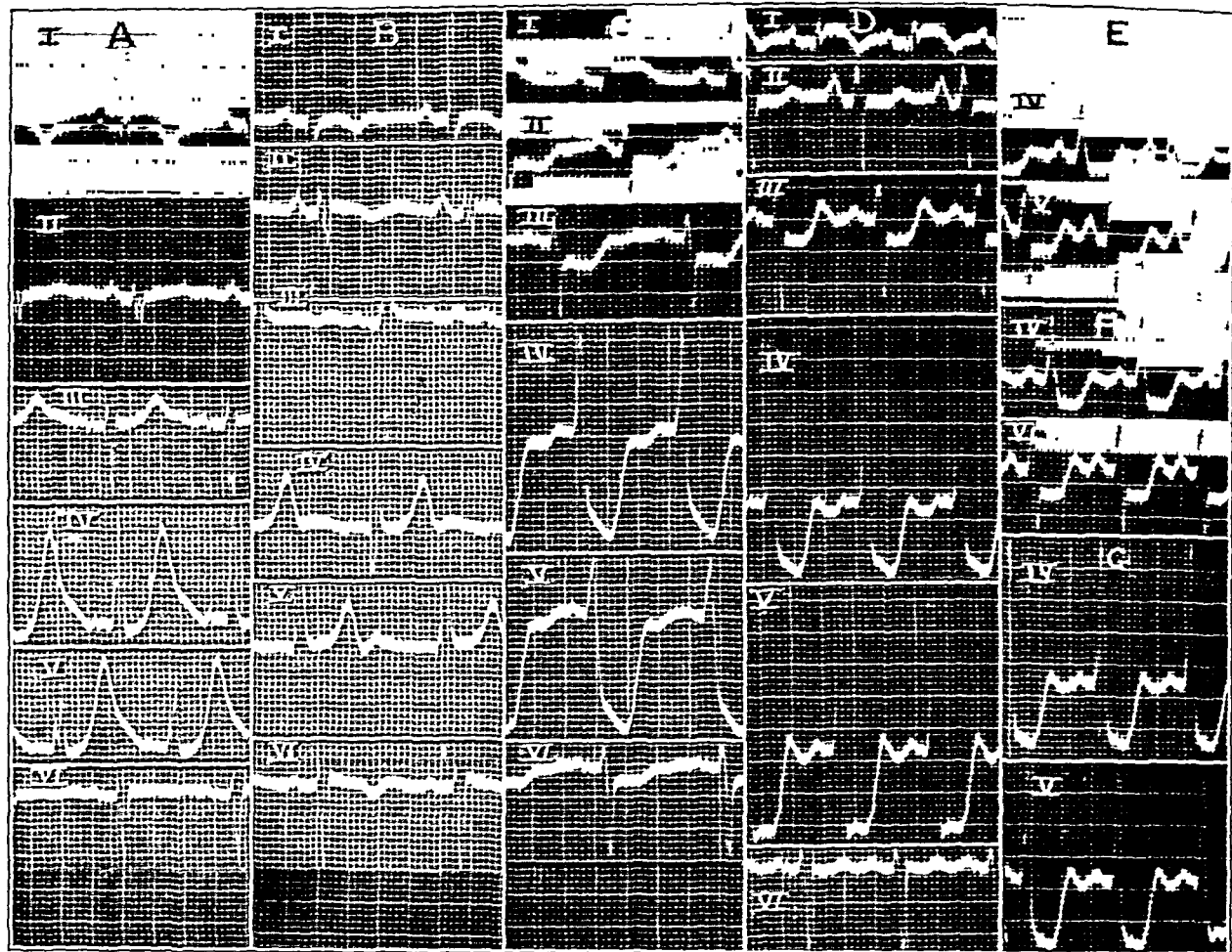


Chart 4.—Electrocardiograms of case 19; an example of group A. The anterior electrode was placed over the apex impulse. Attacks of cardiac pain occurred on Oct. 16, 1932, December 22 and December 28. Necropsy on December 30 showed recent occlusion of the main left anterior descending coronary artery, 1.5 cm. from its origin. In addition, several smaller, less recent infarctions were found in the distribution of this artery.

A, tracing taken on December 24. The inversion of T 1, the absence of the initial downward deflection of Q R S in leads IV and V, and the upright T waves in leads IV and V suggest the presence of an old infarction in the anterior surface of the left ventricle. The unusual height of the T waves in leads IV and V suggest the possibility that a recent small coronary occlusion (on December 22) has been superimposed on the old one (October 16).

B, tracing taken on December 27. The changes which have occurred since the previous tracing was taken strengthen the possibility that a recent small coronary occlusion has occurred. On December 28, at 4 a. m. another much more severe attack of cardiac pain began.

C, tracing taken December 28, six hours after the onset of pain. Definite elevation of the RS-T interval is seen in lead I. Depression of this interval appears in all the other leads. The initial downward deflection of Q R S in leads IV and V is absent.

D, tracing taken December 29. Some changes have taken place since the preceding day. The general features of the tracing are typical of group A.

E, leads IV and V taken December 29, with the anterior electrode at the aortic area.

F, leads IV and V (December 29) with the anterior electrode at the pulmonic area.

G, leads IV and V (December 29) with the anterior electrode in the third inter-space, 4 cm. to the left of the sternum.

Deviations of the RS-T interval are recorded from all these positions, but become more marked as the anterior electrode approaches the point on the wall of the chest lying directly over the infarct. It may be possible in some cases to arrive at a rough estimation of the size of an anterior infarction by determining the size of the area in the precordium from which deviations of the RS-T interval are recordable.

RS-T interval. On the basis of these findings, combined with the history, a tentative diagnosis was made of old anterior and recent posterior infarction.

The patient died suddenly on January 8. Necropsy was performed by Dr. John Bauer on January 8. The heart was moderately dilated. There was an old infarct in the lower third of the anterior surface of the left ventricle. A recent occlusion of the right coronary artery was found, with acute infarction of the entire posterior surface of the left ventricle, not including the apex. There was a mural thrombus on the inner surface of the old infarct.

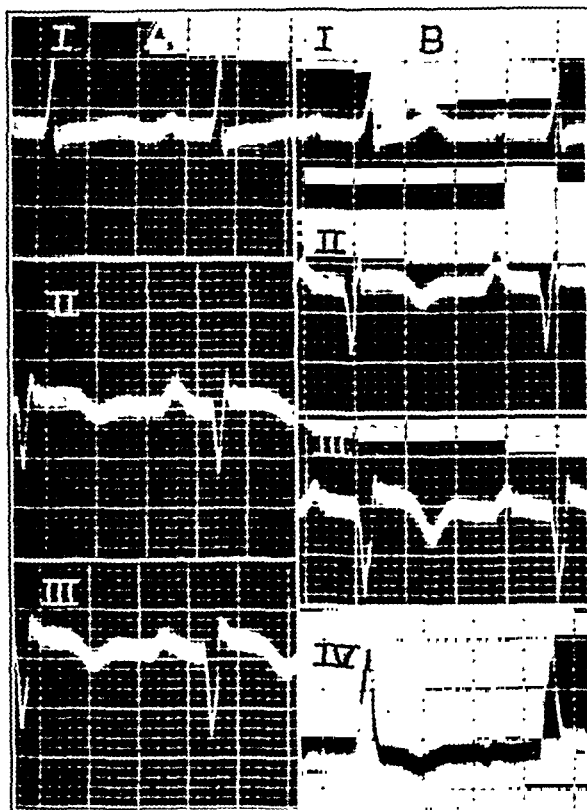


Chart 5.—Electrocardiograms of case 33, an example of group B. The anterior electrode was placed in the fifth interspace, 4 cm. to the left of the sternum. The patient had an attack suggesting coronary occlusion in 1927. Another attack of severe prolonged cardiac pain began on Jan. 4, 1933.

*A*, electrocardiogram taken January 5. Lead I shows little. Lead II shows a deep Q wave and a slight elevation of the RS-T interval. Lead III shows a deep Q wave, a more marked elevation of the RS-T interval and a more definitely inverted T wave. Leads IV, V and VI were not taken. The P R interval is 0.20 second.

*B*, electrocardiogram taken January 7. Leads I, II and III are much the same. The T waves in leads II and III are more definitely inverted. The P R interval is slightly longer (0.22 second). Lead IV shows an absence of the initial downward deflection of Q R S, a slurring of the R wave and a very slight elevation of the RS-T interval. Leads V and VI were not taken.

On the basis of these tracings and the clinical history, a diagnosis of old anterior and recent posterior infarction was made ante mortem. Necropsy confirmed the diagnosis.



*Summary.*—The electrocardiogram of a patient with an old anterior and recent posterior cardiac infarction presented a deep Q wave and an elevation of the RS-T interval in leads II and III. Lead IV showed an absence of the initial downward deflection of Q R S and a slight elevation of the RS-T interval.

#### ELECTROCARDIOGRAPHIC CLASSIFICATION OF CASES

The great majority of our thirty-six cases of acute coronary occlusion fit into one or the other of the following two electrocardiographic groups:

*Group A (Nineteen Cases).*—Examples of this type are shown in charts 2, 3 A, 4, 6, 7 and 8 and in the two cases reported previously.<sup>2a</sup> The characteristics of the group may be defined under the heads of the various leads.

**Lead I:** In the first days the RS-T interval may be elevated. (However, in nine of the nineteen cases, this elevation was absent in at least one tracing during the first week, when chest leads showed definite deviations of the RS-T interval [charts 2, 7 and 8].) The elevation of the RS-T interval soon subsides as a rule, and in most cases inversion of the T wave appears. This change from a deviation of the RS-T interval of one direction to a T wave of the opposite direction usually takes place more rapidly in lead I than in leads IV and V. A Q wave was present in lead I in six of the nineteen cases.

**Lead II:** Usually no deviation of the RS-T interval is seen in this lead. If one appears it is likely to be an elevation (exception case 19, chart 4). The shape and appearance of the T wave is not constant. No findings that can be recognized as diagnostically helpful appear in the later stages; but if the RS-T interval has been elevated in the acute stage, an inversion of the T wave may appear later.

**Lead III:** This lead likewise seldom shows a deviation of the RS-T interval. In occasional cases there is a depression of this interval. The subsequent changes seem nonspecific for diagnostic purposes, in the light of present knowledge.

**Lead IV:** In this lead the findings are more striking<sup>7</sup> than in any other. There is a deep depression of the RS-T interval which usually persists for from five to nine days (i. e., much longer than the elevation in lead I). In the course of time it disappears. A high-peaked, upright T wave develops and tends to remain. The large initial downward deflection of the Q R S complex either disappears completely or is markedly diminished in size. In fourteen of nineteen cases it disappeared completely and did not return in the period during which we

7. The deviations of the RS-T interval and other deflections are probably magnified by the proximity of the anterior electrode to the heart.

were able to follow the patient. In one case it disappeared and returned slightly three months later (case 11). In four cases a small deflection persisted throughout, never more than 2 mm. in depth.

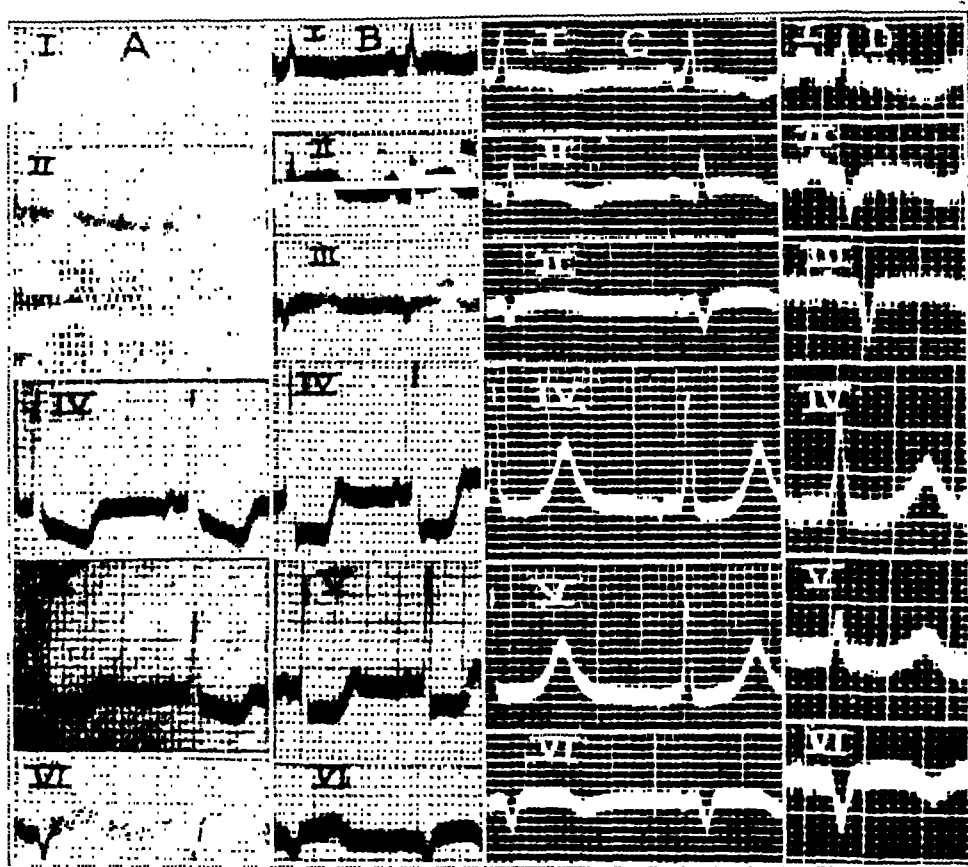


Chart 6.—Electrocardiogram of case 18, an example of group A. The anterior electrode was placed in the fifth interspace 4 cm. to the left of the sternum. Acute coronary occlusion occurred on March 15, 1932. *A*, tracing taken seven days later (March 22). Lead I shows little. Lead II shows an elevation of the RS-T interval. Lead III shows little. Leads IV and V show an absence of the initial downward deflection of QRS and slight depressions of the RS-T interval—(more marked in lead IV). Lead VI is similar to lead III.

*B*, tracing taken on March 24. The limb leads have not changed a great deal. A much more definite depression of the RS-T interval is seen in leads IV and V, again more marked in lead IV.

*C*, tracing taken on March 30. The deviations of the RS-T interval have disappeared and T waves have appeared which are opposite in direction to the original deviations of the RS-T interval.

*D*, tracing taken April 29. The initial downward deflection of QRS in leads IV and V has not returned. These last two tracings (*C* and *D*) show the characteristic findings of the later stages of this type of infarction.

Lead V: The findings in this lead are similar to those in lead IV, but the depression of the RS-T interval is usually less deep. All the complexes may be somewhat smaller.

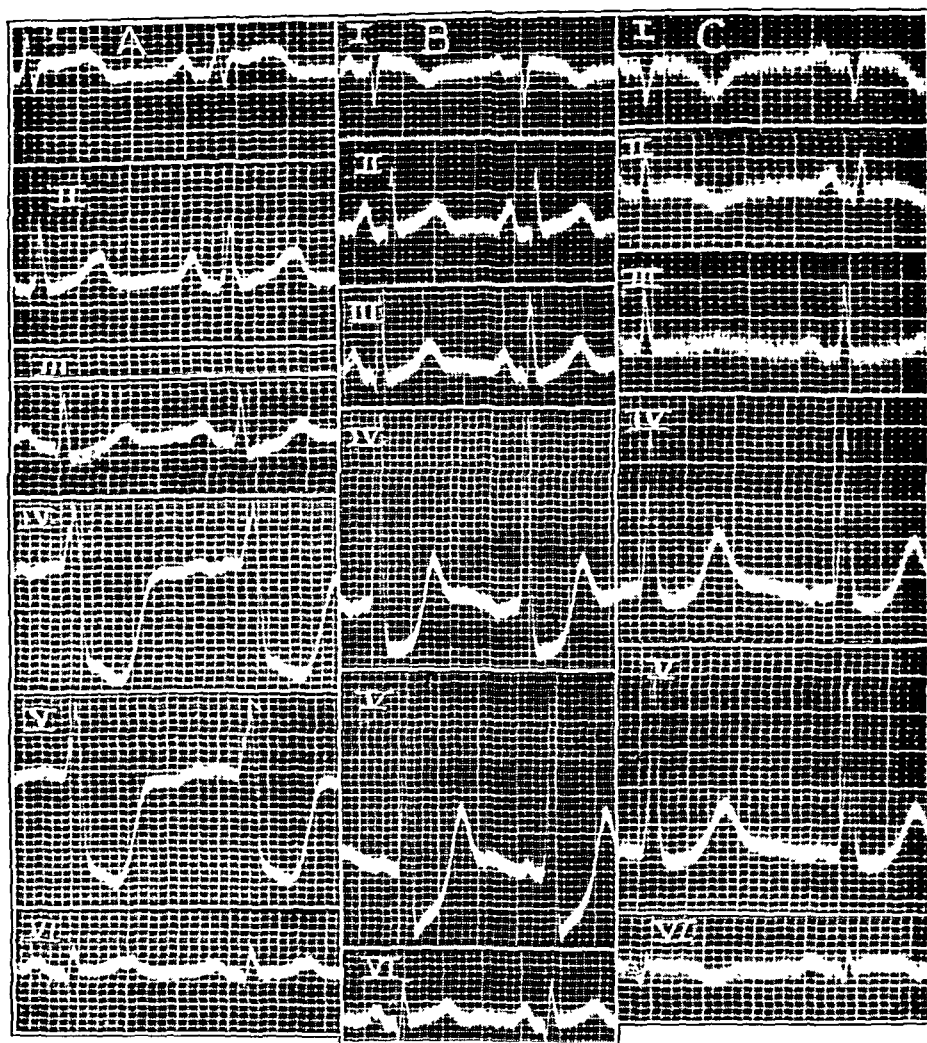


Chart 7.—Electrocardiograms of case 12, an example of group A. The anterior electrode was situated at the apex. Acute coronary occlusion occurred Nov. 10, 1932.

*A*, tracing taken November 10, three hours after the attack. Lead I shows an elevation of the RS-T interval. Lead II shows little. Lead III shows a suggestive depression of the RS-T interval. Leads IV and V show an absence of the initial downward deflection of Q R S and marked depression of the RS-T interval. Lead VI is a rather unsatisfactory replica of lead III.

*B*, tracing taken November 11. There are no deviations of the RS-T interval in the limb leads. The Q R S complex and T wave in lead I have changed since the previous day. Leads IV and V still show marked depressions of the RS-T interval. The T wave is beginning to become upright.

*C*, tracing taken December 5. The deviations of the RS-T interval have practically disappeared. The initial downward deflection of Q R S in leads IV and V has not returned. The inverted T 1 and T 2 and large upright T 4 and T 5 are characteristic of the later stages of this type of infarction.

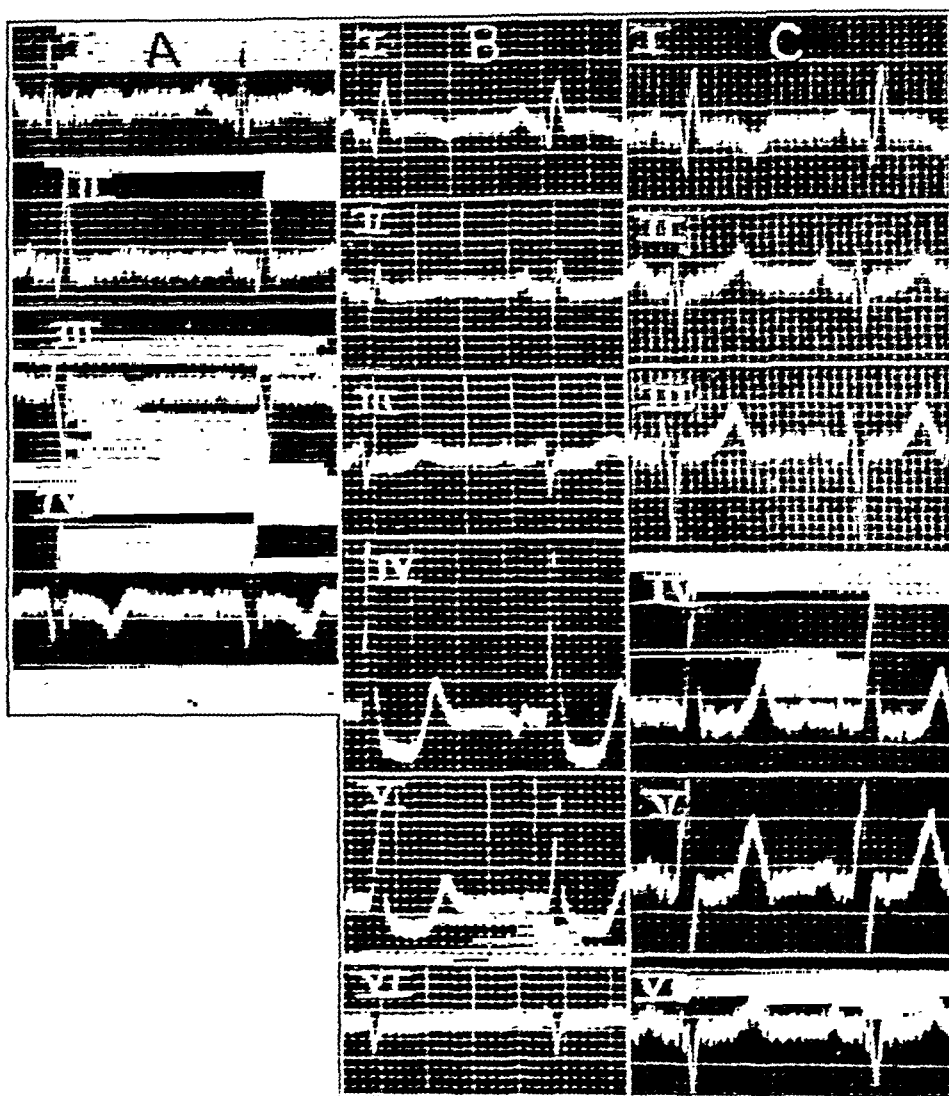


Chart 8.—Electrocardiograms of case 6, an example of group A. The anterior electrode was placed in the fifth left interspace, 4 cm. from the sternum. Acute coronary occlusion occurred on July 21, 1932.

*A*, tracing taken in February, 1932, five months before the attack.

*B*, tracing taken on July 25, four days after the attack. Lead I shows a Q wave and a cove-shaped RS-T interval, but there is no deviation of this interval from the iso-electric line. Leads II and III show little. Leads IV and V show a disappearance of the initial downward deflection of Q R S. Lead IV shows a definite depression of the RS-T interval. Lead V shows much less change in the RS-T interval. T 4 and T 5 are beginning to turn upward. Lead VI shows little.

*C*, tracing taken November 26, four months after the attack, showing the characteristic late findings of this type of infarct. The initial downward deflection of Q R S in leads IV and V has not returned. T 4 and T 5 are upright and large. There are a Q wave and an inverted T wave in lead I.

Lead VI: As a rule, this lead gives no additional information. It often, but not always, resembles lead III.

*Group B (Twelve Cases).*—Examples of this type are shown in charts 5, 9, 10 and 11 and in a previous publication (case 3).<sup>2b</sup> The characteristics of the group are defined under the heads of the various leads.

Lead I: This lead may be entirely normal. If a change in the RS-T interval occurs, it consists of a depression (six or twelve cases) This is usually small.

Lead II: This lead usually shows a Q wave and an elevation of the RS-T interval. The Q wave persists. The elevation of the RS-T interval usually gives way in a few days to a sharply inverted T wave.

Lead III: This lead usually shows the most characteristic changes. There is a deep Q wave (eleven cases) which persists. The twelfth case (case 23, chart 9 B) showed a small Q wave. The RS-T interval is usually elevated in the early stages. After a few days this elevation disappears, and a sharply inverted T wave develops. The negative T wave remains for some time.

Lead IV: This lead often shows no abnormal findings. If a deviation of the RS-T interval appears, it consists of an elevation. Four cases showed slight elevations of the RS-T interval. Three showed upright T waves and two showed absence of T waves. In all but two, the initial downward deflection of Q R S was present, although it was small in four. In the later stages, this lead tends to become normal. In one case (case 32, chart 11) leads IV and V showed an elevation of the RS-T interval, when only a suggestion of such a change was seen in leads II and III. This elevation was more pronounced when the anterior electrode was placed at the apex than when it was situated nearer the sternum.

Lead V: The general statements made about lead IV apply to lead V. It may be normal; any deviations of the RS-T interval are elevations. After the acute phase, the tracing tends to return to normal. However, elevations of the RS-T interval have been more frequent and more pronounced (chart 9) in this lead than in lead IV.

Lead VI: This lead usually resembles lead III, with an elevation of the RS-T interval and a Q wave. Usually, however, these are smaller than in lead III.

It is of interest to note that both in the recent and the old cases in group B, particularly the latter, leads II, III, IV, V and VI tend to resemble one another, with a Q wave and inverted T wave (chart 10).

In group A, the rate of disappearance of the deviations of the RS-T interval, and the completeness of their disappearance tend to parallel the rate and completeness of clinical recovery. In group B, on the

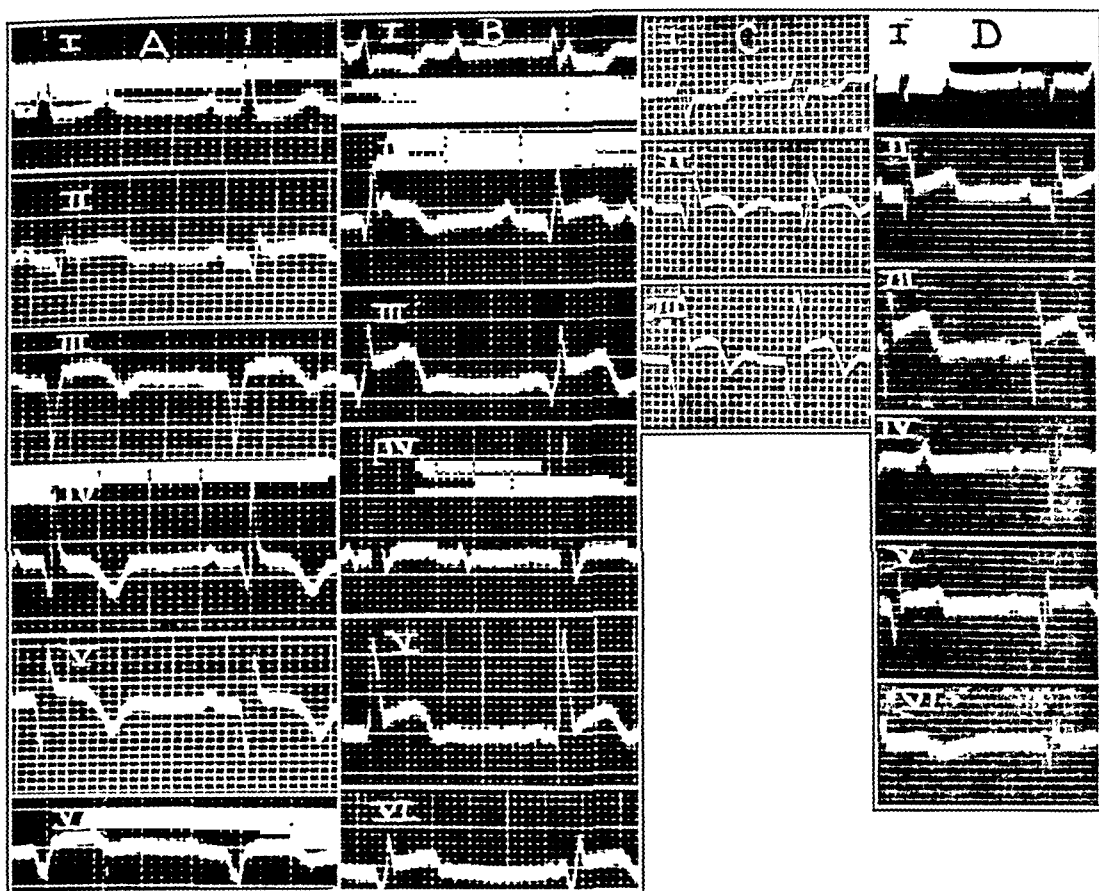


Chart 9.—Electrocardiograms of cases in group B. *A*, electrocardiograms of case 24 taken Oct. 4, 1932, with the anterior electrode in the fifth interspace, 4 cm. to the left of the sternum. Acute coronary occlusion occurred on September 26, eight days previously. Lead I is normal except for a slight suggestion of a depression of the RS-T interval. Lead II shows a Q wave and an elevation of the RS-T interval. Lead III shows a very pronounced Q wave, an elevation of the RS-T interval, and a beginning inversion of the T wave. Lead IV is practically normal. Lead V shows a slight elevation of the RS-T interval; otherwise it is normal. The initial downward deflection of Q R S in leads IV and V is preserved. Lead VI is a poor replica of lead III. Despite the deviations of the RS-T interval, this patient felt subjectively quite well at the time this tracing was taken. He walked into the hospital for the electrocardiogram.

*B*, electrocardiograms of case 23 taken on September 15, with the anterior electrode in the fifth interspace, 4 cm. to the left of the sternum. Acute coronary occlusion occurred on September 13. The patient had a complete heart block. (This disturbance of mechanism occurs in the experimental animal most commonly with occlusion of the left posterior circumflex artery, <sup>1a</sup> which supplies the posterior surface of the left ventricle.) Lead I shows a small depression of the RS-T interval. Lead II shows a Q wave and an elevation of the RS-T interval. Lead III shows Q wave and a marked elevation of the RS-T interval. Lead IV shows no definite elevation of the RS-T interval. Lead V shows a definite elevation of the RS-T interval. Lead VI is a poor replica of Lead III. The patient had a history of a previous attack of coronary occlusion. It seems likely, on account of the absence of the initial downward deflection of Q R S in leads IV and V, that this previous attack was an anterior infarction.

*C* and *D*, electrocardiograms of case 28, with the anterior electrode at the apex beat. Acute coronary occlusion occurred on Jan. 18, 1932. *C*, three leads taken January 19. Lead I shows a slight depression of the RS-T interval. Lead II shows a deep Q wave and an elevation of the RS-T interval. Lead III shows a Q wave and an elevation of the RS-T interval. *D*, taken on January 20, Lead I shows little. Lead II shows a Q wave and an elevation of the RS-T interval. Lead III shows a deep Q wave and a slightly greater elevation of the RS-T interval. Lead IV shows the persistence of the initial downward deflection of Q R S and an upright T wave. Lead V is similar but shows a slight elevation of the RS-T interval (slight elevations of RS-T in leads IV and V are probably more dependable for diagnostic purposes than slight depressions). Lead VI shows a Q wave and a slight elevation of the RS-T interval.

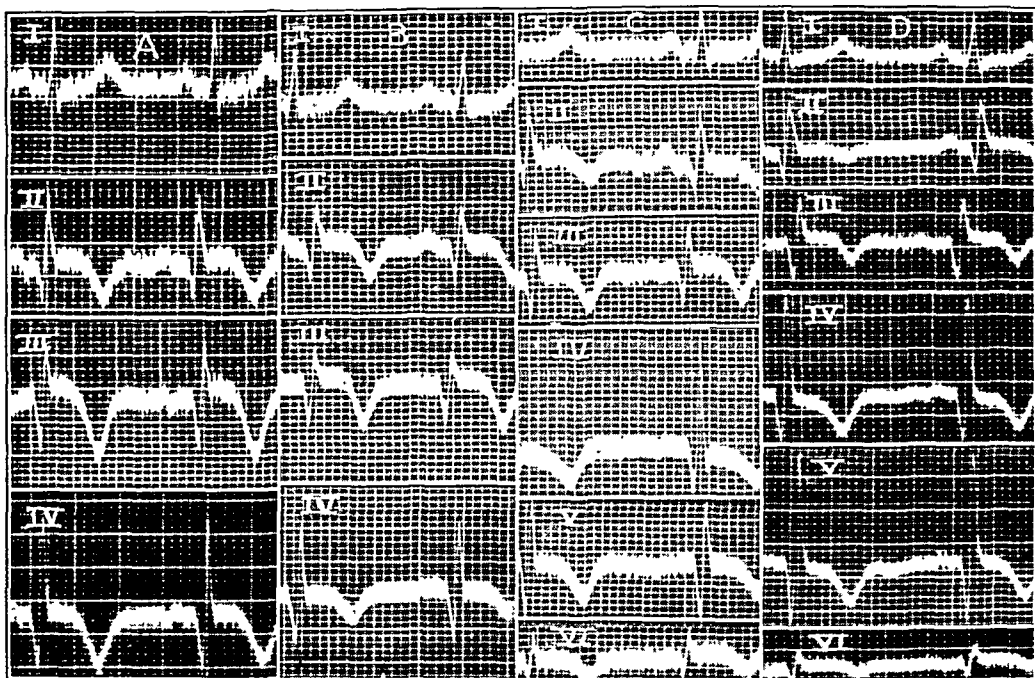


Chart 10.—Electrocardiograms of case 22, an example of group B, with the anterior electrode in the fifth interspace 4 cm. to the left of the sternum. Acute coronary occlusion occurred on Jan. 5, 1932, two days before the first tracing was taken.

*A*, four leads taken on January 7. Lead I shows nothing definite. Lead II shows a Q wave, slight elevation of the RS-T interval and a sharply inverted T wave. Lead III shows a deep Q wave, a definite elevation of the RS-T interval and a sharply inverted T wave. Lead IV is within normal limits. The initial downward deflection is preserved and the T wave is inverted. The presence of a prominent "shoulder" at the end of the RS-T interval in lead IV is suggestive of some abnormality. This patient had recovered considerably in two days and was able to walk into the hospital for the tracing.

*B*, four leads taken on February 9. The general characteristics of the previous tracings are preserved. The deviations of the RS-T interval are smaller, but still suggestive. The shoulder at the end of the RS-T interval in lead IV is less prominent.

*C*, six leads taken on March 15. There is not much change since December 9. Lead VI is a poor replica of lead III.

*D*, six leads taken on September 28, nine months after the attack. Slight elevations of the RS-T interval still persist in leads II, III and IV. Leads I, IV and V are normal. This is an example of the characteristic late findings in group B. Leads II, III, IV, V and VI are somewhat similar in that they possess initial downward deflections and inverted T waves.

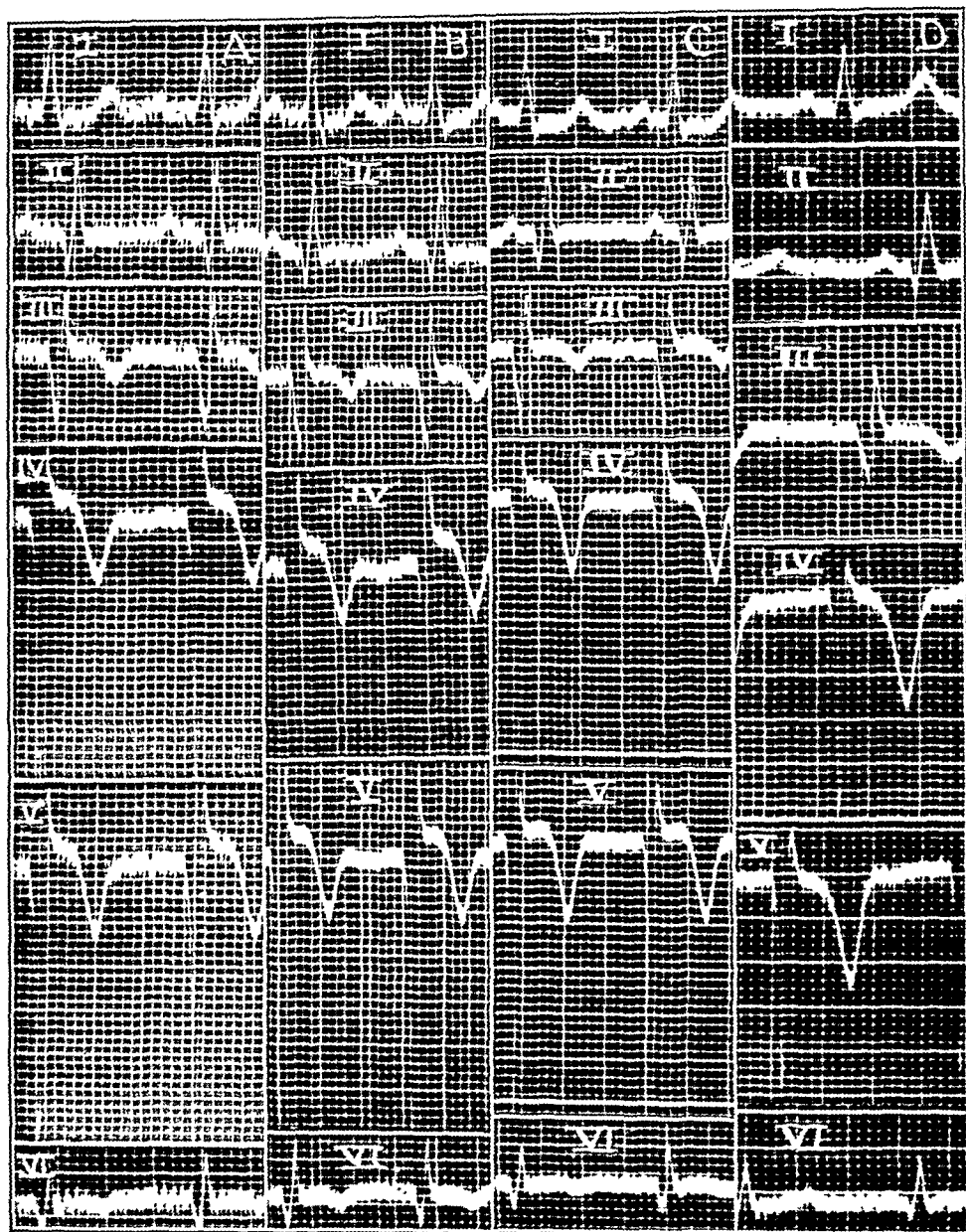


Chart 11.—Electrocardiograms of case 32, an example of group B. The anterior electrode was placed at the apex. Acute coronary occlusion occurred on December 5, 1932.

*A*, tracing taken December 8. There is a suggestion of a depression of the RS-T interval in lead I. Lead II shows a Q wave but no deviation of the RS-T interval. Lead III shows a deep Q wave, a slight elevation of the RS-T interval and an inverted T wave. Leads IV and V show a huge initial downward deflection of QRS, an elevation of the RS-T interval of 3 mm. and a sharp deep T wave. Lead VI shows a Q wave. This is the only case in group B in which chest leads were essential to make the diagnosis of acute infarction.

*B*, tracing taken December 9, showing similar findings.

*C*, tracing taken December 12. The limb leads are much the same. The RS-T interval in leads IV and V has subsided considerably.

*D*, tracing taken, Jan. 6, 1933. Slight change has occurred in the limb leads. The elevations of the RS-T intervals in leads IV and V have disappeared, and the late findings of group B are evident.



*Data on Cases\**

Case	Color	Sex	Age	Date of Recent Occlusion	Date of Electrocardiogram	Group	Initial Downward Deflection of Q R S	RS-T Interval	T wave	Results and Comments
1. M. K.....	W	F	76	9/14/31	9/14/31	A	-----	Previously reported, <sup>2a</sup> case 1	-----	Sudden death 12/16/31
2. G. M.....	W	M	62	10/ 5/31	10/18/31	A	-----	Previously reported, <sup>2a</sup> case 2	-----	Sudden death 4/5/32
3. M. C.....	W	F	52	3/16/32	3/20/32 daily until 3/25/32	A	-----	See chart 2	-----	Sudden death 3/25/32; necropsy showed recent anterior infarction (see text)
4. D. G.....	W	M	42	10/22/32	10/25/32	A	-----	See chart 3A	-----	Death 10/25/32; necropsy showed recent anterior infarction (see text)
5. A. L.....	W	M	55	5/28/32	6/ 4/32	A	-----	See chart 3B	-----	Death 6/5/32; necropsy showed recent anterior infarction (see text)
6. S. S.....	W	M	51	7/21/32	7/25/32	A	-----	See chart 8	-----	Is able to do light work 1/4/33
7. W. E.....	W	M	52	7/14/32	7/21/32	A	Absent in I, II, III and IV; leads V and VI not taken	IV, -3 mm.	I, flat; IV, +5 mm.	Recovered; state of compensation moderately good 1/4/33
8. L. G.....	W	M	46	5/30/32	5/31/32 and daily after that for 10 days	A	Absent in all six leads	I, coveplane, no deviation; IV, -4 mm.; V, -3 mm.	I, sharply negative	
					6/ 2/32		Absent in all six leads	I, slight elevation; IV, -7 mm.; V, -6 mm.	.....	Actively markedly restricted; angina on effort
					11/ 7/32 (last tracing)			RS-T deviations in IV and V persisted until 6/7/32		
							Absent in all six leads	No deviation	I, negative; IV and V, +2 mm.	
9. R. A.....	W	M	70	5/11/32	5/13/32	A	I, present; IV and V, absent	I, +1 mm.; IV, -4 mm.; V, -3 mm.	.....	Has marked restriction of activity; can walk 2 blocks (friction rub 5/12/32 at apex)
					10/30/32		Same	No deviation	I, negative; IV and V, +2 mm.	

10. T. D.....	W	M	60	11/ 7/32	11/12/32	Δ	I, present; IV and V, absent	I, no deviation; IV, -2.5 mm.; V and VI, not taken	I, negative; IV, markedly diphasic, -3 mm. and +4 mm.	Recovered sufficiently to return to work on a farm
11. H. H.....	W	M	62	12/ 6/31	12/ 8/32	Δ	Same	IV, -1 mm.	IV, still diphasic; -1 mm. and +6 mm.	
12. M. G.....	W	M	56	11/10/32	12/16/31	Δ	I and IV, absent; V and VI, not taken	I, no deviation; IV, -2 mm.	I, negative; IV, +4 mm.	Died March, 1932; showed congestive failure throughout; tracing
13. M. D.....	C	F	52	9/16/32	11/10/32	Δ	IV, returned slightly, -1.5 mm.	I, no deviation; IV, -1 mm.	I, flat; IV, +3 mm.	Recovering slowly and inadequately 1/8/33
14. M. B.....	W	M	62	2/27/32	9/27/32	Δ	I, absent; IV and V, -0.5 mm.	I, no deviation; IV, -4 mm.; V, -3 mm.	I, flat	Died suddenly 9/28/32
15. W. B.....	W	M	59	11/17/32	3/ 6/32	Δ	I, present; IV and V, -0.5 mm.	I, +1 mm.; III, -0.5 mm.; IV, -3 mm.; V, -1 mm.	.....	Discharged 3/29/32 on the verge of congestive failure
16. J. K.....	W	M	41	10/ 5/32	11/20/32	Δ	IV and V, absent	I and III, no deviation; IV, -3 mm.; V, -2 mm.	I, negative; IV and V, +5 mm.	
17. F. F.....	W	M	53	10/23/32	10/14/32	Δ	I, IV and V, absent	I, +1.5 mm.; II, +1 mm.; IV and V, -5 mm.	I, upright; IV and V, +2 mm.	Connalescing 12/2/32
				10/29/32	11/8/32	Δ	Same	No deviation	I, negative; IV and V, diphasic	Marked restriction of activity 11/8/32
				11/ 1/32		Δ	I, IV and V, absent	I, curved upward; III, -1 mm.; IV and V, -3 mm.	I, negative; IV, +4 mm.; V, +5 mm.	On the verge of congestive failure 11/26/32
						Δ	Same	I and III less deviation	.....	

\* In order to conserve space in the table, the following abbreviations are used: The Roman numerals I to VI designate the leads. Following these numerals there are Arabic numerals with minus or plus signs preceding them. These signify the amplitude and direction of RS-T interval deviations from the iso-electric line. The amplitude and direction of T waves are indicated in a similar way.

*Data on Cases—Continued*

Case	Color	Sex	Age	Date of Recent Occlusion	Date of Electrocardiogram	Initial Downward Deflection of Q R S	RS-T Interval	T wave	Results and Comments
17. N. F.....(Continued)					11/ 3/32	Same	I and III, no deviation; IV and V, -2 mm.	I, negative; IV and V, +4 mm.	
					11/ 9/32	Same	IV and V, -2 mm.	I, -2 mm.; IV and V, +8 mm.	
18. D. F.....	W	M	58	3/15/32	3/22/32	A	See chart 6		Not heard from since 4/29/32; marked restriction of activity
19. W. B. B...	W	M	54	12/22/32 12/28/32	12/24,27, 28/32	A	See chart 4		Died 12/30/32; full report in paper
20. P. S.....	W	M	56	1/12/32	1/13/32	Some- what like A	Previously reported, <sup>2b</sup> case 1		Died in an attack of pulmonary edema 6/10/32; never recovered compensation
21. E. A. V...	W	M	63	9/19/32	9/20/32	Like A in I and III	I, curved upward; III, suggestive depression; IV and V, no deviation	IV and V, -4 mm.	Died 10/26/32
				9/22/32	9/24/32	Like A in I and III	I, +2 mm.; III, -2 mm.; IV and V, no deviation	Same	
22. R. S.....	W	M	43	1/ 5/32	1/ 7/32	B	See chart 10		Pain began in the back; back at regular work; recovered almost completely
23. W. W. R..	W	M	62	9/13/32	9/15/32	B	See chart 9B		Had had a previous attack of coronary occlusion; 12/15/32, activity markedly restricted
24. E. R.....	W	M	61	9/26/32	10/ 4/32	B	See chart 9A		Nine days after attack walked into hospital feeling quite well
25. M. L.....	W	F	63	2/17/32	2/28/32	B	Previously reported, <sup>2b</sup> case 3		Died with right hemiplegia (embolus ?) 3/3/32
26. M. H.....	W	M	65	9/21/31	9/28/31	B	III, curved upward; IV, +0.5 curved upward		On 10/3/32 was working at dentistry on a slightly reduced schedule; good recovery

27. E. M.....	W	F	57	12/27/31	12/28/31 (only limb leads)	B	II, absent; III, deep IV and V, present Same III, IV and V, present	I, -2 mm.; II, no deviation; III, +2 mm. IV, no deviation; V, +1 mm.; VI, +0.5 mm. No deviation	I, diphasic; III, upright IV, +1 mm.; V, +2 mm. I, II and III, slightly inverted; IV and V, flat	1/18/32, moderate restriction of activity
28. M. K.....	W	M	50	1/18/32	1/7/31 1/18/31	B	II, III and VI, deep; IV and V, small II, III and VI, deep; IV and V, -3 mm. Deep in III, IV, V and VI	I, -1 mm.; II, +2 mm.; III, +3 mm.; IV, +2 mm. No deviations	II and III, upright; IV and V, inverted II and III, upright	Died 1/25/32 from what was thought to be a mesenteric embolus Discharged 6/28/32; says he feels just as well as before attack
29. W. R.....	W	M	51	5/16/32	5/18/32	B	II, III, IV, V and VI, deep	..... I, slight depression; II and III, +1 mm.; IV and V, no depression II and III, +1 mm.	Flat in all leads II and III, inverted; IV, diphasic; V, normal II, III, IV, V and VI, inverted II, III, IV and VI, inverted	Discharged 10/22/32; exercise tolerance moderately restricted Effort angina on discharge 11/9/32
30. L. O.....	W	M	48	9/25/32	6/11/32	B	II, III, IV, V and VI, deep	..... I, curved upward; III and VI, +1.5 mm.; IV and V, no deviation	See chart 11	
31. H. K.....	W	M	74	10/23/32	10/30/32	B	Same	See chart 5	See chart 5	Conalescing satisfactorily 1/15/33
32. H. C.....	W	M	48	12/5/32	10/29/32	B	II, III, IV, V and VI, deep	See chart 3C	See chart 3C	Full report in paper; died 1/8/33
33. H. R.....	W	M	61	1/4/33	12/8/32	B		I, suggestion of slight depression, -1 mm.; III and VI, suggestion of slight elevation, +1 mm.; IV and V, normal	II and III, upright; IV and V, flat	Died 6/16/32; full report in paper Result unknown
34. J. S.....	W	M	67	6/7/32	1/5/33	B		Previously reported, <sup>2b</sup> case 2		
35. A. H.....	W	F	51	4/12/32	6/12/32	B				
36. L. S.....	W.....	M.....	50	11/6/31	11/6/31	B (?)	II and III, absent; IV and V, present			
										Died suddenly, 11/6/31

other hand, although the extreme changes in the RS-T interval subside rapidly, slight deviations may persist for a long time in the face of what appears to be a fairly complete clinical recovery (case 22, chart 10).

In addition to these two main electrocardiographic groups, various other isolated types were seen. The electrocardiogram in case 20 resembled those in group A, but had little or no depression of the RS-T interval in leads IV and V and a marked elevation of this interval in leads I and II. The tracing in case 21 showed a high RS-T interval in lead I, a depression of this interval in lead III and no deviation in any of the other four leads. The electrocardiogram in case 36 resembled those in group B in certain respects, but was too bizarre to be considered a typical example.

Finally, the tracings in cases 34 and 35 showed no change in the RS-T interval in any lead. In case 34 (chart 3 C) there occurred a small infarction at the extreme apex of a heart which was the seat of previous extensive infarction. The tracing was not taken till six days after the attack. In the other case (35) the clinical diagnosis of coronary occlusion was fairly certain. The patient eventually recovered. A slight suggestion of elevation of the RS-T interval in lead III was the only pertinent electrocardiographic finding. Only one tracing was obtained for this patient, twelve hours after the onset.

*Summary.*—One might say that with a few exceptions our cases belong to one or the other of two electrocardiographic groups:

Group A consists of nineteen cases. The main electrocardiographic finding is a deep RS-T interval and a disappearance of the initial downward deflection in leads IV and V. This may or may not be accompanied by an elevation of the RS-T interval in lead I. The later findings are a subsidence of these deviations of the RS-T interval, the appearance of T waves of opposite sign and the continued absence of the initial downward deflection of Q R S in leads IV and V.

Group B consists of twelve cases. The main findings are a deep Q wave in lead III and an elevation of the RS-T interval, rapidly giving place to a sharply inverted T wave. Leads II and VI often show similar features. In leads IV and V the normal initial downward deflection of Q R S persists. If deviations of the RS-T interval appear in these two leads, they consist of elevations, not depressions. They are more common in lead V than in lead VI. They are occasionally seen in leads IV and V, when not clearly present in the limb leads, especially when the anterior electrode is situated at the apex (case 32, chart 11).

The electrocardiographic findings characteristic of group A probably indicate infarction of the anterior surface of the left ventricle, usually including the apex and the anterior portion of the interventricular septum, due to occlusion of the left anterior descending coronary artery.

The evidence for this statement may be summed up as follows: (a) The RS-T interval and T wave changes in the limb leads in group A are those which Barnes and Whitten<sup>8</sup> considered to be dependent on anterior infarction. (b) The deviations of the RS-T interval in the six leads resemble in general those seen in tracings of the dog after ligation of the left anterior descending coronary artery.<sup>1</sup> (c) Wilson and co-workers<sup>9</sup> stated that changes in the Q R S complex of this type are seen in patients who show anterior infarcts at necropsy. (d) Four of our cases in group A have come to necropsy and have shown recent anterior infarction (cases 3, 4, 5 and 19).

The electrocardiographic findings in group B probably indicate infarction of the posterior surface of the left ventricle resulting from occlusion of the right coronary artery. The following evidence supports this statement: (a) The changes in the RS-T interval and T wave in the limb leads in group B are those which Barnes and Whitten<sup>8</sup> considered to be dependent on posterior infarction. (b) The deviations of the RS-T interval in the six leads resemble in general those seen in tracings of the dog after ligating vessels supplying the posterior surface of the left ventricle.<sup>1</sup> (c) Fenichel and Kugell<sup>10</sup> and Wilson and his co-workers<sup>9</sup> stated that changes in the Q R S complex of the group B type are seen in patients showing posterior infarction at necropsy. Moreover, Wilson and co-workers<sup>9</sup> stated that "when there was an elevation of the S T segment in lead III, this occurred in the precordial leads also." (d) One case in group B came to necropsy, and showed a recent posterior infarction (case 33).

#### COMMENT

Chest leads have occasionally clinched the diagnosis in the cases in group B (case 32). However, their greatest usefulness seems to be in group A, since the deviations in the RS-T interval are almost always more pronounced and more persistent in leads IV and V than they are in the limb leads. It is our belief that most of the cases which have been electrocardiographically missed heretofore have probably been cases of anterior infarction.

The tracing gave evidence of acute coronary occlusion in the first examination of all but one of our patients for whom electrocardiograms

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8. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *Am. Heart J.* **5**:142 (Dec.) 1929.

9. Wilson, F. N.; Barker, P. S.; MacLeod, A. G., and Klostermyer, L. L.: The Electrocardiogram in Coronary Thrombosis, *Proc. Soc. Exper. Biol. & Med.* **29**:1006, 1932.

10. Fenichel, N. M., and Kugell, V. H.: The Large Q-Wave of the Electrocardiogram: A Correlation with Pathological Observations, *Am. Heart J.* **7**:235, 1931.

were made during the first five days. Thus the necessity for repeated tracings on successive days for diagnostic purposes is diminished by the use of chest leads in addition to limb leads. Nevertheless, we have seen patients (cases 19, 20 and 21) whose acute coronary occlusion was only suggested by the first tracing, whereas the tracing taken subsequently showed convincing evidence of the lesion. In all three of these patients the clinical findings suggested that the original infarct had been small. Moreover, subsequent symptoms pointed to an extension of the occlusion to other arteries between the taking of the first and the second tracings. However, it is not improbable that cases occur in which the area of anoxemia dependent on the occlusion of a certain vessel becomes temporarily enlarged. This might be due to (1) depression of the general circulation,<sup>11</sup> (2) temporary constriction of anastomosing coronary arteries, (3) reduction in pulmonary ventilation resulting from abdominal distention or (4) displacement of the heart in such a way as to impair coronary flow.<sup>12</sup> In such cases, without actual extension of the occlusion to other vessels, the lesion might at one time give no definite electrocardiographic findings, whereas at another time it might produce typical deviations of the RS-T interval.

Although no final analysis is possible at this time, it might be worth while to discuss the advisability of using each of the three chest leads. It is theoretically possible to multiply the number of chest leads ad infinitum with relatively little proportional increase in the information gained. A great deal of confusion could be produced by such a step. It seems to us, therefore, that the statement should be made that lead VI is often much like lead III, and that it has added nothing, so far, in the study of the patients in this series. However, its further use in cases of posterior infarction is necessary before it is entirely discarded.

Leads IV and V are undoubtedly useful. However, the question arises as to whether one of them could be discarded and only the other used. The evidence we have might be stated as follows: Leads IV and V are very similar for normal persons. For patients with heart disease without acute infarction these leads are also apt to be much alike. Nevertheless, for many patients with presumable anterior infarction, the

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11. Feil, H. S.; Katz, L. N.; Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischaemia, *Am. Heart J.* **6**:522 (April) 1931.

12. This suggestion is based on the fact that when the experimental animal is placed in certain positions, the heart seems to twist on its pedicle of great vessels, and deviations of the RS-T interval appear. We have suspected that this was due to an angulation of one of the coronary arteries and a consequent impediment to the flow of blood through that vessel. It has seemed to us possible that this might occasionally occur in man. In fact, in certain patients with anginal pain, the assumption of the left lateral position seems to be a factor in the production of an attack.

depression of the RS-T interval is more marked in lead IV than in lead V (charts 6 and 8), and the contour of the T wave is often quite different in the two. On the other hand, in cases of supposed posterior infarction (chart 9 B) there is often an elevation of the RS-T interval in lead V when none appears in lead IV. In our series of cases, one or the other of these two leads, in addition to the limb leads, would have sufficed to make the diagnosis. Nevertheless, we feel that it is reasonable to continue the use of both for the present.

Other chest leads, beside the three we have used as a routine, have not given additional information in any case thus far. However, when confronted with a patient in whom a recent coronary occlusion is suspected clinically, and for whom no diagnostic findings appear in the six leads, it would seem reasonable to attempt to bring out deviations of the RS-T interval by the use of other chest leads. Moving the anterior electrode to different points on the precordium should probably be the first procedure to consider.

Evidence is accumulating to show that it may be possible to locate the general position of an infarct in the heart by means of the electrocardiograph. Barnes and Whitten<sup>8</sup> have done the pioneer work in this field. Since their observations have been published, it has become evident that the electrocardiograph, as used in the past, is limited in its capacity to localize infarcts. In the first place, a certain group of cases have appeared in which no prediction of location has been possible because of the absence of localizing signs. In the second place, a small group of cases has been reported in which the location predicted from the electrocardiograph was proved wrong at necropsy.<sup>13</sup> By using chest leads, the first group of cases can probably be reduced in number. Further study is necessary before one can tell whether the second group will persist despite the use of chest leads.

From the standpoint of the localization of infarcts, the deviations in the RS-T interval seem to be of primary importance in the early stages of the disease. However, as Wilson and co-workers<sup>9</sup> pointed out, the significance of alterations in the Q R S complex must not be overlooked. In the first place they serve to corroborate the information derived from deviations in the RS-T interval in the acute stage. In the second place, they tend to persist, whereas the deviations of the RS-T interval are usually transitory. In group A (probably anterior infarction) the normal initial downward deflection of Q R S in leads IV and V was absent in fifteen of nineteen cases. In the other four this deflection was small, less than 2 mm. in amplitude. In only two of our cases in which this deflection was absent has it reappeared, despite the

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13. Gilchrist, A. R., and Ritchie, W. T.: Ventricular Complexes in Myocardial Infarction and Fibrosis, *Quart. J. Med.* **23**:273, 1930.



fact that five of our patients have been followed for periods varying from three to seven months. In six cases a Q wave was present in lead I. In group B (probably posterior infarction) the initial downward deflection has tended to persist in leads IV and V, and a deep Q wave has been present in lead III in every case but one (case 23, chart 9 B). This wave also occurs in leads II and VI in most instances. Thus several months after a coronary occlusion the findings in the Q R S complexes and T waves may point to the nature of an antecedent attack. Chart 8 C illustrates the late findings in anterior infarction, and chart 10, those in presumable posterior infarction.

In three of our cases of acute coronary occlusion there were electrocardiographic evidences of previous infarction. In case 3 (chart 2) there was electrocardiographic and necropsy evidence of previous posterior infarction. Case 33 (chart 5) showed electrocardiographic and necropsy evidence of previous anterior infarction. Case 23 (chart 9 B) showed suggestions in the electrocardiograph of previous anterior infarction, but as necropsy was not performed this suspicion was not confirmed. Such findings may have a prognostic significance.

Before the subject of electrocardiographic localization of cardiac infarction is dismissed, it might be well to call attention to certain inherent limitations in the method which help to explain certain inconsistencies in the findings of groups A and B:

1. The occlusion of a certain artery in the human heart cannot be expected to give the same electrocardiographic picture in every patient for the following reasons: (a) The type of electrocardiogram obtained probably depends on the relative positions of the heart, with its infarct, and the electrodes. Changes in the position of the heart in the experimental animal cause definite changes in the electrocardiographic features of a given infarct.<sup>14</sup> Therefore, when one considers the variable size, shape, axis and position of the human heart, it becomes obvious that an infarct in a certain location in the heart may vary in its electrocardiographic manifestations in minor ways. (b) The electrocardiographic characteristics of an acute infarct may be altered by changes in the Q R S complex caused by a previous infarction (case 3, chart 2, and case 33, chart 5). (c) The obstruction of a given coronary artery may produce ischemia of a much larger area than usual because of previous obstruction or occlusion of other coronary arteries. (d) The anatomic variation to which the coronary arteries are subject is another factor which may be responsible for unexpected electrocardiographic results.

2. The electrocardiographic findings in acute coronary occlusion are probably dependent on the exact size and location (with reference to the

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14. Unpublished observations.

electrodes) of the ischemic area in the heart. One cannot determine with certainty at necropsy the exact size and shape of this area during life. It may have been much greater than the pathologic lesion and may have varied considerably from time to time, depending on the efficiency of (a) the general circulation, (b) the respiration and (c) the condition of the adjacent coronary circulation.

3. Marked deviations of the RS-T interval are probably produced by injured (living) muscle. When this injured muscle dies, the deviations of the RS-T interval probably disappear. If, therefore, the heart is the seat of a large infarct, in which the major portion of the involved heart muscle is dead, relatively small deviations of the RS-T interval might be recorded by the electrocardiograph (case 5). After a coronary occlusion has been present for several days, the obtainable deviations in the RS-T interval are probably produced by muscle situated at the periphery of the lesion, rather than by the main infarcted muscle mass. Therefore, unless one has obtained a tracing within a short time after the onset, one cannot say that the recorded deviations of the RS-T interval were caused by ischemic heart muscle located as the pathologic lesion is located. The main infarcted muscle mass may be dead and incapable of giving rise to deviations of the RS-T interval. For this reason, electrocardiographic studies of cardiac lesions produced with a cautery<sup>15</sup> must probably be interpreted with a certain degree of caution, especially if these lesions are large.

In the cases reported in this paper, there has been a difference in prognosis between the two groups, A and B. Of the nineteen patients in group A, eight have died of cardiac failure, eight are markedly restricted by their lesions, two have moderate restriction of activity, and one is almost as well as before the attack. Of the twelve cases in group B, four have made a practically complete recovery; three have slight restriction of activity, two are markedly restricted (one of these had a previous attack), and three have died, two probably as a result of embolus, not from cardiac failure. No definite opinion concerning prognosis should be formed until a large group is studied, and until more complete information is available as to localization. Nevertheless, it is coming to be our impression that the symptoms from a posterior infarction, when compared with an anterior one, are often less dramatic and less prolonged; that the immediate prognosis in the attack is less grave, and that subsequent recovery of adequate cardiac function is apt to be more rapid and more complete.

It has been the opinion of clinicians that occlusion of the left anterior descending artery is much more common than occlusion of any

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15. Crawford, J. H.; Roberts, G. H.; Abramson, D. I., and Cardwell, G. C.: Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, *Am. Heart J.* 7:627 (June) 1932.

other coronary artery. On the other hand, a recent pathologic study by Barnes and Ball <sup>16</sup> shows a somewhat similar incidence of anterior and posterior infarction. If, as suggested in the previous paragraph, there is really a clinical and prognostic difference between the two, the divergence of opinion, just referred to, might be explainable in one of two ways: 1. Clinicians may be right. Anterior infarction may be the more common. The greater frequency of death in the acute attack and the marked cardiac disability of the survivors may have tended to prevent patients with anterior infarction from reaching the institution where Barnes and Ball made their studies. Their series may therefore represent an involuntarily selected group. 2. Clinicians may be wrong. There may be a nearly equal incidence of anterior and posterior infarction. The erroneous belief that anterior infarction is the more frequent may have arisen as follows: Patients with this lesion are more profoundly ill and remain incapacitated for a longer time. Consequently, more of them consult the heart specialist or are admitted to the hospital, and are reported in the literature from these sources. On the other hand, the patients with posterior infarction are more often treated by the family physician at home, and make a smaller showing in the literature, except in studies of a group of consecutive unselected necropsies. It should be possible to decide on the merits of the first of these two explanations by pathologic studies from other sources, made in a way similar to those of Barnes and Ball.

We have occasionally encountered a patient with a presumable posterior infarction in whom the major part of the pain was located posteriorly and in the arms (case 22). Moreover, certain patients with anterior infarction have pain in the precordium and in the left upper quadrant of the abdomen. Thus far, however, the situation of the pain has not proved a reliable guide to the location of the infarct.

A reduction of blood pressure has usually been considered as one of the cardinal signs of acute coronary occlusion. However, in certain of our patients the blood pressure has been quite high for the first twelve hours, and a drop has not appeared until the next day. This phenomenon is probably well known to those who see a number of such patients, but it has not been sufficiently emphasized in the literature.

#### SUMMARY

Thirty-six cases of acute coronary occlusion are reported, in which chest leads as well as limb leads were used in the electrocardiographic study.

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16. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, *Am. J. M. Sc.* **183**:215 (Feb.) 1932.

Three chest leads were used: lead IV, from the lower precordium to the angle of the left scapula; lead V, from the lower precordium to the left leg, and lead VI, from the angle of the left scapula to the left leg.

The exact location of the anterior chest electrode is important in determining the contour of the electrocardiogram. This has not been true in the case of the posterior electrode.

The methods used in taking chest leads and the normal findings in leads IV, V and VI are discussed.

Certain variations which have been seen in pathologic cases without acute cardiac infarction are described.

Deviations in the RS-T interval may occur in chest leads in the absence of acute coronary occlusion.

An electrocardiographic analysis of our thirty-six cases shows that thirty-one of them tend to fall in one or the other of two groups, termed for convenience groups A and B.

Group A consists of nineteen cases. Examples of this group are shown in charts 2, 3, 4, 6, 7 and 8. Four cases in this group which have come to necropsy have shown occlusion of the left anterior descending coronary artery, with infarction of the anterior surface of the left ventricle, usually including the apex and the anterior half of the inter-ventricular septum.

Group B consists of twelve cases. Examples of this group are shown in charts 5, 9, 10 and 11. The data at hand suggest that these are cases of infarction of the posterior wall of the left ventricle due to occlusion of the right coronary artery.

When chest leads as well as limb leads were used, all but one of our cases of acute coronary occlusion showed electrocardiographic evidence of the lesion during the first few days. The absence of deviations of the RS-T interval in all six leads renders the diagnosis of recent coronary occlusion quite unlikely.

Certain characteristic alterations produced in the Q R S complex as a result of coronary occlusion tend to persist. Thus several months after a coronary occlusion has taken place the findings in the Q R S complexes and T waves may point to the nature of an antecedent attack.

There are certain indications that the symptoms of a posterior infarction, when compared with those of an anterior one, are often less dramatic and less prolonged; that the immediate prognosis is less grave, and that the subsequent recovery of adequate cardiac function is apt to be more rapid and more complete.

NOTE.—Since this article was submitted for publication there have been several further developments: The patient in case 8 died of acute cardiac failure on June 5, 1933. Necropsy showed an organized thrombus obstructing the left anterior descending coronary artery, 2 cm. from its

origin. There was a large fibrosed infarct in the anterior surface of the left ventricle, not involving the apex to any great extent. The anterior four fifths of the interventricular septum showed extensive endocardial scarring. The patient in case 15 died of cardiac failure in December, 1932. Permission for necropsy was not obtained. However, roentgenographic studies of the heart made prior to death by Dr. Ralph Bromer clearly showed an aneurysm protruding from the left border of the heart, in the region supplied by the left anterior descending coronary artery. Two other cases not published in this paper have come to necropsy. Their electrocardiograms showed the typical findings of group A. Pathologic examination showed occlusion of the left anterior descending coronary artery, with a large infarct in the anterior surface of the left ventricle in each case.

Thus the location of the infarct has been determined in eight cases in group A. In all eight the lesion has been situated in the interior surface of the left ventricle, in the distribution of the left anterior descending coronary artery.

# A SIMPLE METHOD OF PRODUCING VASODILATION IN THE LOWER EXTREMITIES

WITH REFERENCE TO ITS USEFULNESS IN STUDIES OF  
PERIPHERAL VASCULAR DISEASE

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Recent advances in the surgery of the sympathetic nervous system have made it increasingly necessary to develop a simple method for determining early in the course of peripheral vascular disease whether the diminished flow of blood to an extremity is due to simple arterial spasm or to obliterative structural disease of the blood vessels. The several tests now in use, though different in method, are similar in principle. The surface temperature of the distal portion of the cool, exposed extremity is measured thermo-electrically. Dilatation of the peripheral vessels is then produced, and the rise in surface temperature is recorded. The level to which the temperature rises with complete vasodilatation has been determined in persons with normal peripheral circulation. If the surface temperature fails to reach this normal level in a room at suitable temperature, the arteries supplying the part are regarded as being unable to dilate owing to organic changes in their walls.

We<sup>1</sup> observed that immersing the forearms and hands in warm water produced vasodilatation in the lower extremities. In ten observations made on the spontaneously cool lower extremities of six normal subjects the temperatures of the toes began to rise within fifteen minutes after the forearms were immersed in warm water. In all but one of these observations the surface temperature reached 32 C. (89.6 F.) within twenty-nine minutes after the forearms were immersed. In every instance the surface temperature exceeded 31.5 C. (88.7 F.), which

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From the Robinette Foundation of the Hospital of the University of Pennsylvania.

1. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J. Clin. Investigation* **11**:1019, 1932.

Morton and Scott<sup>2a</sup> regarded as the minimum normal response to spinal and general anesthesia. It appears, therefore, that the vasodilatation induced by this procedure is comparable to the vasodilatation resulting from nerve block, general anesthesia or spinal anesthesia.

To produce vasodilatation by this relatively simple procedure requires no special apparatus and causes much less discomfort to the patient than the injection of typhoid vaccine or the induction of spinal or general anesthesia. We also described studies made on three patients who presented symptoms and signs of peripheral vascular disease. These studies illustrated the possible usefulness of this procedure in differentiating spasm from organic occlusion. The vasodilator response to warming the forearms and hands compared favorably with the vasodilatation produced in one patient by spinal anesthesia and in another by the intravenous injection of typhoid vaccine. The present paper describes the vasodilator response to warming the forearms and hands obtained in twenty-four patients with vascular disturbances involving the lower extremities. In eleven patients some other method of producing maximal vasodilatation was also employed, and the results have been compared with those obtained by immersing the forearms in warm water.

#### METHOD

Most of the observations were made on ambulatory patients who were seated with the legs extended so that the feet could rest comfortably on a stool about 15 inches (about 37 cm.) high. The room temperature was read from a mercury thermometer or a thermal junction suspended in the air near the toes. The feet and legs from a point just below the knees were exposed to the air of the room. The surface temperature of the toes was determined thermo-electrically, the thermal junctions being placed in contact with the skin on the dorsal surface of the distal phalanx just proximal to the base of the nail. In some instances the junctions were bare; in others a single layer of adhesive plaster covered the junction without modifying the results significantly. The skin temperature was read at intervals of two minutes while the exposed extremities cooled; when it had become sufficiently low, usually 26 C. (78.8 F.) or less, the forearms were immersed to the elbows in warm water the temperature of which was between 43 and 45 C. (between 109.4 and 113 F.). For this purpose ordinary white enameled arm baths, 52 cm. long, 20 cm. wide and 15 cm. deep, were entirely satisfactory. The temperature of the water was kept between 43 and 45 C. by means of a small electric heating coil placed beneath each bath. While the forearms were immersed the skin and room temperatures were read every minute.

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2. Morton, J. J., and Scott, W. J. M.: (a) Methods for Estimating the Degree of Sympathetic Vasoconstriction in Peripheral Vascular Diseases, *New England J. Med.* **204**:955, 1931; (b) The Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, *J. A. M. A.* **97**:1212 (Oct. 24) 1931; (c) Sympathetic Activity in Certain Diseases, Especially Those of the Peripheral Circulation, *Arch. Int. Med.* **48**:1065 (Dec.) 1931; (d) Some Angiospastic Syndromes in the Extremities, *Ann. Surg.* **94**:839, 1931.

Certain patients (cases 2, 9, 10, 13 and 20) were confined to bed. The head of the bed was elevated so that the patient assumed a semirecumbent position. The arm baths with the electric heating coils beneath them were placed on boards laid on the bed beside the patient. The forearms and hands could be completely immersed without discomfort. The lower extremities were exposed to the air and were examined in the usual way.

In normal subjects it was found that the skin temperature of the toes began to rise within fifteen minutes or less and reached 32 C. (89.6 F.) within twenty-nine minutes after the forearms were immersed in warm water. In the observations described in this article the forearms were immersed continuously for thirty-five minutes, a period definitely longer than that required for a complete vasodilator response in normal subjects. However, when the temperature of the toes reached 32 C. before the total period of thirty-five minutes had elapsed the observation was, in some cases (e. g., case 1, fig. 1) terminated, since the full normal response had been obtained and nothing was to be gained by prolonging the period of immersion. The color of the skin was estimated according to the scale devised by Lewis.<sup>3a</sup>

#### OBSERVATIONS

1. *Normal Vasodilator Responses in Patients with Pain, Coldness, or Cyanosis of the Lower Extremities.*—This group of patients all presented certain symptoms which are frequently associated with deficient circulation in the lower extremities; none of them had ulcers or gangrene. In some of these patients the cause of the pain, coldness or cyanosis was relatively clear, but this simple test proved useful in showing the diminished circulation could not be due to obliterative structural disease of the arteries, since the peripheral vessels were able to dilate normally

The normal vasodilator response observed in this group of patients is illustrated in figure 1, which shows the details of an observation on the patient in case 1, who suffered from varicose veins and chronic thrombophlebitis.

CASE 1.—O'M., a white man, aged 52, was admitted to the University Hospital on April 23, 1932, with a chief complaint of "swelling of the legs." He had had varicose veins for many years, with painless swelling of the right ankle for four years. In October, 1931, he experienced a sudden, severe, dull pain in the calf of the right leg. The pain was continuous and was neither relieved nor made worse by movement or rest. In December, 1931, the same symptoms appeared in the left leg. In January, 1932, the right leg began to swell from below upward, and in March the left leg swelled also. The patient had observed blueness of the toes since February, 1932.

Physical examination showed edema of both legs and thighs, the right lower extremity being slightly larger throughout than the left. Both feet were mod-

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3. Lewis, T.: (a) Standard Colours for Use in the Study of Vascular Reactions of Human Skin, *Heart* **15**:1, 1929; (b) Experiments Relating to Peripheral Mechanism Involved in Spasmodic Arrest of Circulation in the Fingers, a Variety of Raynaud's Disease, *ibid.* **15**:7, 1929.



erately cyanotic. Neither posterior tibial artery could be palpated. The pulsation of the left dorsalis pedis artery was felt, but the right was impalpable, owing probably to the greater edema on the right side. Roentgen examination of the feet revealed no evidence of arteriosclerosis, but numerous phlebolites were found on both sides. Venous pressure was measured indirectly by the capsular method of Krogh, Turner and Landis.<sup>4</sup> With the patient in the recumbent position, venous pressure amounted to 24 cm. of water in the right foot and to 17 cm. of water in the left.

The details of the vasodilator response are shown in table 1 and figure 1. The temperature of the toes, originally 26.4 C. (79.5 F.), fell gradually to 24 C. (75.2 F.) on exposure to the air of a room with a temperature varying between 18 and 19 C. (between 64.4 and

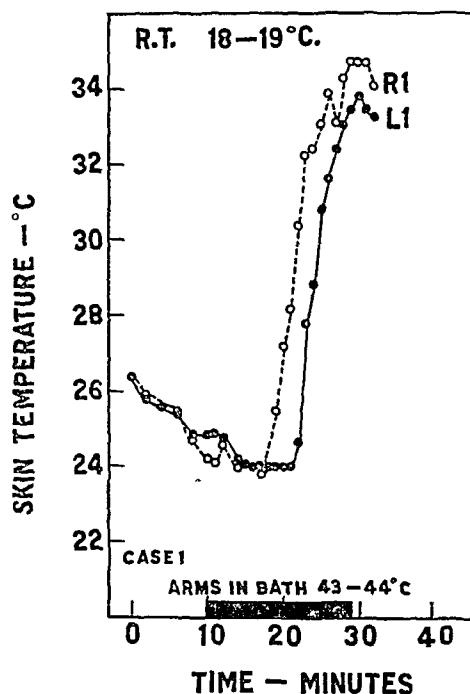


Fig. 1.—Normal vasodilator response observed in a patient (case 1) with bilateral thrombophlebitis. In this figure and in subsequent figures *L1* and *R1* indicate the skin temperature of the left and right great toes respectively; *R.T.*, the room temperature. The shaded area below indicates the period during which the forearms were immersed in warm water.

66.2 F.). At this time the color of the right and left great toes was X. Immersing the forearms in baths at a temperature of from 43 to 45 C. was followed by a feeling of warmth and, after five minutes, by perspiration first over the forehead and later over the entire body including the feet. Ten minutes after the forearms were immersed the color of the right great toe was VI, and that of the left great

4. Krogh, A.; Turner, A. H., and Landis, E. M.: A Celluloid Capsule for Measuring Venous Pressures, *J. Clin. Investigation* **11**:357, 1932.

TABLE 1.—*Normal Vasodilator Responses in Patients with Pain, Coldness or Cyanosis of the Lower Extremities*

Case	Sex	Age	Side	Diagnosis	Pain	Coldness	Cyanosis	Arterial Pulse			Room Temperature, C.	Vasodilator Response				Temperature at End of Period of Immersion, C.
								Posterior Tibial	Dorsalis Pedis			Toes Observed	Initial Temperature of Toes, C.	Time From Immersion to Beginning of Rise, Minutes	Time to Reach 32 C., Minutes	
									Not palpable	Not palpable						
1	M	52	R	Chronic thrombophlebitis, bilateral	+	++	+	Not palpable	Not palpable	Not palpable	19.0	R 1 R 3 L 1	24.1 23.8 24.8	9 12 13	13 17 17	34.7 34.3 33.5
2*	F	25	R	Normal.....	None	None	None	Palpable	Palpable	Palpable	22.0	R 1 L 1 L 3	29.1 24.9 24.0	5 10 13	6 16 22	36.3 34.3 33.2
3	M	30	R	Congenital arteriovenous fistula, phlebittis	+++	None	+++	Palpable	Palpable	Palpable	23.0	R 1 R 3 L 1 L 3	23.1 23.2 20.8 20.6	7 7 7 7	11 14 12 14	33.9 33.8 35.4 34.5
4	M	51	R	Congenital arteriovenous fistula	None	None	++	Palpable	Palpable	Palpable	11.5	R 2 L 2	19.0 19.8	5 5	15 11	32.2 33.2
5	M	21	R	Sciatic neuritis.....	++	None	None	Palpable	Palpable (?)	Palpable (?)	24.0	R 1 R 3 L 1 L 3	26.7 26.7 27.3 26.9	8 7 7 7	11 11 10 11	34.3 33.6 35.0 33.7
6	M	44	R	Sciatic neuritis, traumatic	++++	++	+++	Palpable	Palpable	Palpable	22.0	R 1 R 3 L 1	31.4 31.1 32.1	5 5 3	3 4 ..	34.1 33.5 35.8
7	M	35	R	Atrophic arthritis, bilateral	++	+++	++	Palpable	Palpable	Palpable	15.0	R 3 L 3	20.9 22.5	9 7	15 10	32.8 33.7

\* This patient suffered from subacute bacterial endocarditis. The rectal temperature at the time of examination was 38.5 C. (101.3 F.).

toe, VII. The temperature of the right great toe began to rise definitely by the ninth minute after the immersion of the forearms; the left great toe began to warm by the thirteenth minute. The temperatures were both above 32 C. seventeen minutes after the forearms were immersed. The observation was terminated nineteen minutes after the forearms were immersed, since a completely normal response had been obtained.

The details of similar responses obtained in seven patients with various conditions are shown in table 1, which gives the sex, age and diagnosis for each patient and also the relative severity of the pain, coldness or cyanosis (graded from + to + + + +). The details of the vasodilator responses are shown to the right. In any one observation the room temperature did not vary more than a degree above or below the average figure recorded. The initial temperature of the toes refers to the skin temperature at the time the forearms were immersed in warm water. Preceding this the lower extremities were exposed to the air of the room so that the toes might become cool before the vasodilator response was elicited. The column headed "Time from Immersion to Beginning of Rise" refers to the period elapsing between the time when the forearms were immersed and the time when the temperatures of the toes had risen 1 degree centigrade (1.8 degrees Fahrenheit) above the initial temperature. Elevations of temperature less than 0.5 C. (0.9 F.) were found to have little significance in normal subjects. When the skin temperature rose 1 C., however, the vasodilator response had always definitely started, and the skin temperature continued to rise more or less rapidly until the maximum was reached. The time required for the skin temperature to reach 32 C. is also shown to amplify data previously published. The skin temperature observed at the end of the period of immersion is recorded for comparison with data in tables 2 and 3.

The room temperature was usually kept between 19 and 24 C. (between 66.2 and 89.9 F.). It required from three to thirteen minutes necessary to lower it before the extremities began to cool. The fact that even then the skin temperature eventually rose above 32 C. is of interest, since it indicates that the complete vasodilator response can be obtained at low as well as at high environmental temperatures. When cold, the toes showed colors of the skin between VIII and XII (Lewis scale). Within from five to ten minutes after the forearms were immersed the patients felt warmer and began to perspire. The color of the skin at the tips of the toes rapidly changed to VI, or even V, when vasodilatation began. This was followed within a few minutes by the rise in temperature, though, as will be mentioned later, in the presence of organic obstruction the color of the skin may change without an increase in skin temperature.

The initial temperature of the toes varied between 19 and 32.1 C. (between 66.2 and 89.8 F.). It required from three to thirteen minutes for the skin temperature to rise 1 C. above the level observed at the time of immersion. In general, though not without exception, the time required for the rise to begin was shorter when the initial skin temperature was higher. The exceptions may have been due to slight grades of obstruction, which, though not great enough to make the response abnormally low, were sufficient to cause a slight delay (e. g., case 1, left). The figures for this group are, however, entirely within the range of variation previously observed in normal subjects. The toes all warmed to 32 C. usually within fifteen minutes after the forearms were immersed, but four of the twenty-one digits examined required from sixteen to twenty-two minutes to reach 32 C. The longest time observed in a normal subject was twenty-nine minutes. The maximum temperature reached during the period when the forearms were immersed varied between 32.2 and 35.8 C. (between 90 and 96.4 F.) in afebrile patients, while in one febrile patient (case 2) the highest skin temperature was 36.3 C. (97.3 F.).

The results obtained in this group of patients permit only one conclusion, namely, that the symptoms or signs present cannot be ascribed to organic narrowing of the arteries. In the patient in case 2 there was good reason to believe that an arterial embolism had caused the disappearance of the posterior tibial pulsation in the left foot, but in view of the normal vasodilator response it must be concluded that collateral circulation was adequate to maintain the nutrition of the tissues. In the absence of any evidence of structural disease of the arteries the cyanosis in the patients in cases 1, 3 and 4 was ascribed to the high venous pressure and the resultant engorgement of the subpapillary venous plexus to which the color of the skin is due. This elevated venous pressure was not sufficient, however, to prevent an adequate flow of blood to the tissues. The patients in cases 5 and 6 were Jewish and were of the age group in which thrombo-angiitis obliterans is a diagnostic possibility. The normal responses excluded organic obstruction. Case 7 illustrates the vascular spasm which frequently accompanies atrophic arthritis. In such varied conditions, therefore, as thrombophlebitis, sciatic neuritis, arteriovenous fistula and arthritis, the reactions to warming were such that the cyanosis, coldness and pain could not be ascribed to a diminished flow of blood due to obliterative structural disease of the arteries.

2. *Vasodilator Responses in Patients with Thrombo-Angiitis Obliterans.*—The vasodilator response to immersing the forearms in warm water was tested in five patients with thrombo-angiitis obliterans, as illustrated in figures 2 (case 8) and 3 (case 10).

CASE 8.<sup>5</sup>—Ga., a white woman of Jewish ancestry, aged 31, had been suffering for the past three years from coldness and blueness of the right foot, with intermittent claudication and cramps in the right leg. Typical migratory phlebitis had occurred in the right leg during the first year after the onset of the symptoms. The toes of the right foot were habitually cold. Except for some coldness of the foot she had experienced no symptoms in the left extremity. The patient used tobacco excessively in the form of cigarettes. A right femoral periarterial sympathectomy performed in October, 1931, had produced no symptomatic improvement.

Physical examination in March, 1932, yielded no findings of importance except those in the lower extremities. Both feet were cold to the instep. At first the toes of the right foot were conspicuously blanched, while those of the left foot

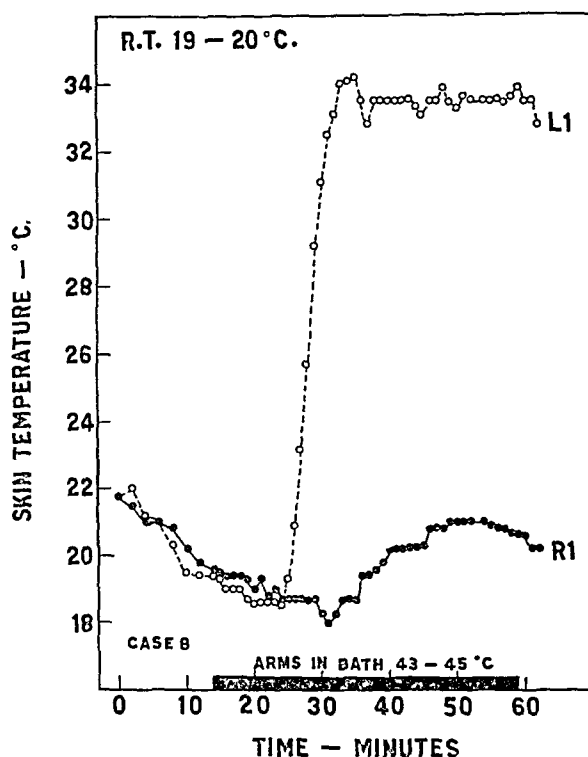


Fig. 2.—Vasodilator response in a patient with thrombo-angiitis obliterans (case 8). The skin temperature rose normally on the left but only slightly on the right.

were normal in color. The patient was seated with the feet supported about 15 inches from the floor. The color gradually returned to the right foot, and cyanosis, which was at first slight (color  $X\frac{1}{2}$ ), became complete (color XIV) in the course of ten minutes. The color of the left foot was normal in the dependent position. Pulsation was felt in the dorsalis pedis and posterior tibial arteries of both feet.

Thermal junctions were fixed to the dorsal surfaces of the distal phalanges of the right first and second toes and the left first toe. As is shown in figure 2, the skin temperature on both sides, originally 22 C. (71.6 F.), gradually fell during twenty minutes to room temperature, which was between 19 and 20 C. (between

5. Dr. Alfred Stengel permitted us to report this case and Dr. Lee Rademaker supplied determinations of the vasomotor index.

66.2 and 68 F.). The forearms were then immersed in water baths maintained at a temperature of from 43 to 45 C. Five minutes later the patient felt warm and began to perspire. The skin temperature of the left great toe began to rise twelve minutes after the immersion of the arms and reached a maximum of 34.2 C. (93.5 F.)—a normal reaction. Simultaneously the color of the right foot brightened, finally becoming pink (colors V to VI). The surface temperatures of the right toes began definitely to rise twenty and thirty-two minutes after immersion of the arms and reached maxima of 21 C. (69.8 F.) for the right first toe and 23 C. (73.4 F.) for the right second toe—a conspicuously abnormal reaction. In this test the forearms were immersed for forty-five minutes. It can be seen in figure 2 that no further rise in temperature occurred during the last ten minutes of the period of immersion.

The history and physical findings were typical of thrombo-angiitis obliterans. The response to immersion of the arms in hot water showed a high grade of

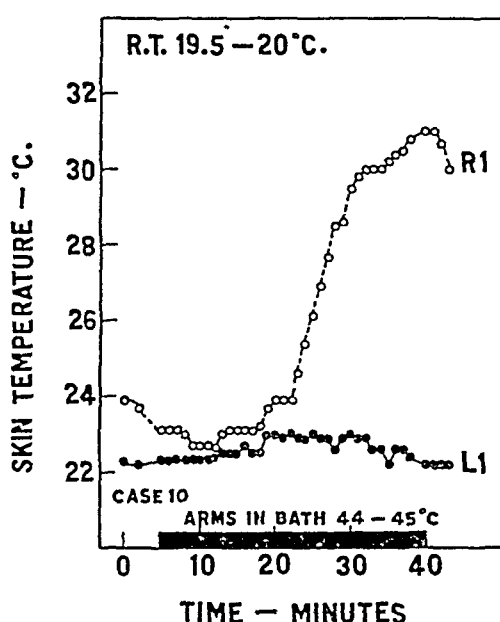


Fig. 3.—Vasodilator response in a patient in an advanced stage of thrombo-angiitis obliterans (case 10). The response was practically absent in the left foot and was only partial in the right foot.

organic occlusion in the vessels of the right leg. The coldness of the opposite leg was necessarily ascribed to spasm in view of the normal rise in temperature obtained when vasodilatation was induced. These findings agree with the vasomotor index determined in this patient by Dr. Lee Rademaker some months earlier. The index for the right foot was 2.5, and that for the left was 3.3, indicating that the symptoms on the right side were due largely to organic occlusion, while the coldness of the left foot was due to simple spasm.

Figure 3 shows the results of the same procedure in a patient with more advanced thrombo-angiitis obliterans.

CASE 10.—Ju., an Italian man, aged 33, was admitted to the University Hospital in April, 1932, complaining of pain in the left foot. During December, 1931, the sole and dorsum of the left foot had become constantly painful, with exacerbations in cold weather and after activity. At times the patient experienced in the

right calf the constricting type of pain characteristic of intermittent claudication. The left foot was occasionally edematous. The right foot and calf were sometimes slightly painful.

Positive physical findings were limited to the extremities. The feet were cold, and the skin was thickened. Elevating the feet produced blanching, which, after the legs were again dependent, persisted longer in the left foot. When the left leg was dependent the toes became deeply purple, the cyanosis extending well over the instep. The right foot was only slightly cyanotic. The right dorsalis pedis could be felt clearly. The left dorsalis pedis and both posterior tibial arteries were not palpable.

As is shown in figure 3, immersing the forearms in warm water induced vasodilatation in the right foot, but the rise in temperature was delayed (beginning after eighteen minutes) and partial, since the great toe warmed only to 31 C. (87.8 F.), while, as is shown in table 2, the temperature of the second toe reached only 24.7 C. (76.4 F.). No response could be detected in the left toes. It appeared, therefore, that the blood vessels of the left leg were conspicuously involved by organic changes, while those of the right were only slightly involved. A test of the vasomotor index yielded values of 1.3 for the right toes and 0 for the left.

The vasodilator responses observed in five patients with thromboangiitis obliterans are summarized in table 2. In two cases (8 and 12) the skin temperature rose above 32 C. in one extremity while showing no change or only a partial rise in the other extremity. As is usually the case, both extremities cooled equally when exposed to the air, but when vasodilatation was induced the diminished flow of blood in the more seriously affected extremity was seen to be due to organic obstruction, whereas in the other extremity the vessels, while tending to go into spasm, were still capable of dilating. In the other three cases (9, 10 and 11) the absent or partial vasodilator response indicated organic obstruction to the flow of blood in both extremities.

In three patients (cases 8, 9 and 11) the vasodilator response to warming the forearms was tested more than once. It may be seen in table 2 that the results obtained in the same patient are qualitatively similar, although the initial temperature of the toes and that of the room were sometimes different. On two occasions the patient in case 9 showed no response in either lower extremity. On three occasions the patient in case 8 showed a complete or an almost complete absence of response in the right foot and an entirely normal response in the left foot. On two occasions the patient in case 11 showed no response in the right foot and only a partial response in the left foot. Accurate quantitative comparisons are impossible unless the successive observations are carried out at a constant room temperature. However, in spite of unavoidable seasonal variations in environmental temperature, the results of repeated observations showed good qualitative agreement.

3. *Vasodilator Responses in Patients Showing Arteriosclerosis.*—Patients with arteriosclerosis have been grouped into two categories:

TABLE 2.—Vasodilator Responses in Patients with Thrombo-Angiitis Obliterans

Vasodilator Response																
Case	Sex	Age	Date of Examination	Side	Pain	Coldness	Cyanosis	Ulcers or Gangrene	Arterial Pulse			Room Temperature, C.	Toes Observed	Initial Temperature of Toes, C.	Time From Immersion to Beginning of Rise, Minutes	Temperature at End of Period of Immersion, C.
									Posterior Tibial	Dorsalis Pedis						
8	F	31	March, 1932	R	+++	+++	+++	None	Palpable	Very faintly palpable	19.2	R 1	19.6	32	..	20.6
				L	None	None	None	Palpable	Palpable	19.0	R 2	19.0	20	..	21.8	
				..	.....	.....	.....	.....	.....	20.0	R 1	19.6	..	..	18.5	
				..	.....	.....	.....	.....	.....	20.0	R 3	18.9	..	..	18.0	
9	M	26	Feb. 1932	R	+++	+++	++	Gangrene	Not palpable	Not palpable	17.0	R 3	22.9	..	..	22.2
				L	++	+++	++	Gangrene	Not palpable	Not palpable	20.0	L 3	21.8	..	..	20.6
				..	.....	.....	.....	.....	.....	20.0	L 4	20.8	..	..	20.0	
				..	.....	.....	.....	.....	.....	20.0	R 2	25.0	..	..	24.0	
10	M	33	April, 1932	R	+	+++	+	None	Palpable	Palpable	20.0	R 1	23.1	18	..	31.0
				L	+++	+++	+++	None	Palpable	Not palpable	25.7	R 2	21.6	23	..	24.7
				..	.....	.....	.....	.....	.....	25.7	L 1	22.3	..	..	22.2	
				..	.....	.....	.....	.....	.....	25.7	L 2	22.2	..	..	21.6	
11	M	58	June, 1932	R	+++	+++	+++	None	Not palpable	Palpable	18.8	R 1	27.1	..	..	27.4
				L	None	+++	None	None	Not palpable	Not palpable	18.8	L 1	27.4	8	..	31.4
				..	.....	.....	.....	.....	.....	18.8	R 1	23.6	..	..	22.5	
				..	.....	.....	.....	.....	.....	18.8	R 3	24.4	..	..	24.1	
12	M	34	June, 1932	R	++	++	+++	None	Not palpable	Not palpable	27.2	R 5	23.5	..	..	23.2
				L	None	None	None	None	Not palpable	Not palpable	27.2	L 1	23.5	21	..	25.6
				..	.....	.....	.....	.....	.....	27.2	L 3	23.4	18	..	25.0	
				..	.....	.....	.....	.....	.....	27.2	R 1	29.2	13	..	30.5	
13	M	34	June, 1932	R	++	++	+++	None	Not palpable	Palpable	27.2	R 3	28.5	8	..	30.5
				L	None	None	None	None	Not palpable	Not palpable	27.2	L 1	29.7	5	8	33.9
				..	.....	.....	.....	.....	.....	27.2	L 3	28.7	7	12	32.5	
				..	.....	.....	.....	.....	.....	27.2	L 3	28.7	7	12	32.5	



(a) those without diabetes and (b) those with diabetes. Figure 4 illustrates the findings in the patient in case 13 whose symptoms were ascribed to simple arteriosclerosis.

CASE 13.—Za., a Jewish man, aged 53, was admitted to the University Hospital in June, 1932, complaining of pain in the left leg. He had been well until 1930, when, according to his statement, he suffered a "stroke," with paralysis of the right leg and left arm. Practically complete power had returned to the affected extremities by the time he was admitted to the hospital. During January, 1932, he experienced pain in the left leg while walking. The pain came on gradually, disappeared with rest and reappeared on further exertion. It was always confined to the left leg and ankle. At this time the right leg had never been painful. During a period of four weeks before admission the pain had become worse. He had used cigarets excessively for many years but had recently reduced the number to ten or less per day.

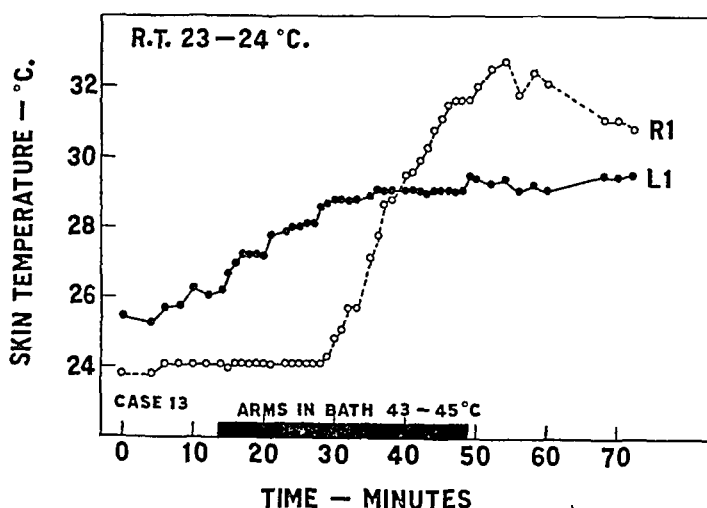


Fig. 4.—Vasodilator response in a patient with arteriosclerosis (case 13). The response was partial in the left foot and was much delayed in the right foot.

On examination the patient had a blood pressure of 165 systolic and 80 diastolic. The heart was slightly enlarged to the left, and a systolic apical murmur was present. Both lower extremities were cold at a room temperature of 24 C. The dorsalis pedis artery was felt on the right side but not on the left. Neither posterior tibial artery was palpable. The right foot was pale but showed no trophic changes. The left toes, however, were moderately cyanotic (color X). Under the nail of the great toe the skin was tender and extremely cyanotic (color XIV). The skin of the left toes was dry, thick and fissured. Roentgen examination showed calcification of the vessels of both legs.

The vasodilator response in the left leg, as shown in figure 4, was incomplete, reaching a maximum of 29.5 C. (85.1 F.). The right toes warmed very slowly, the first toe finally reaching a temperature of 32 C., though not within the thirty-five minute period of immersion. This indicated that the vessels of both lower extremities were organically diseased, though those of the left leg were more severely affected.

Table 3 *a* summarizes the findings in five additional cases of arteriosclerosis. With one exception (patient 17) both extremities were affected. In patient 13, although the temperature of the right great toe finally reached 32 C., it did so only after the abnormally long period of thirty-six minutes. Frequently, also, the rise in temperature began at a later time than normal. It is noteworthy that the most pronounced diminution in response was usually found in patients with ulcers.

The complete absence of a vasodilator response in a patient with arteriosclerosis, diabetes and gangrene is illustrated in figure 5 (case 21).

CASE 21.—B1., an Irishman, aged 46, was admitted to the University Hospital in January, 1932, suffering from diabetes mellitus with gangrene involving the toes of the right foot. One year before admission the patient had been treated elsewhere for an infected callus on the left foot. In November, 1931, the right foot became swollen, red and tender, and the diagnosis of diabetes mellitus was

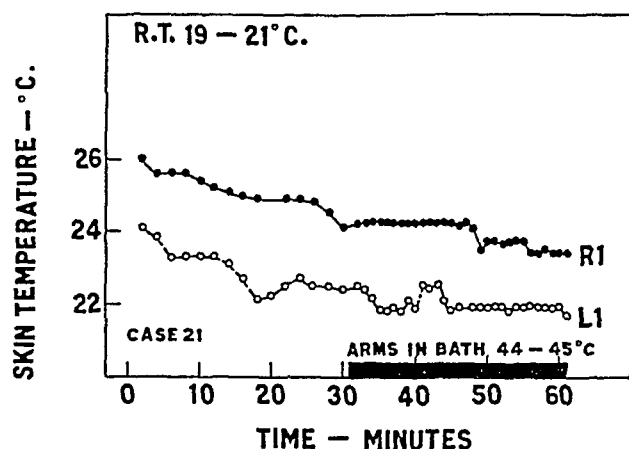


Fig. 5.—Chart showing complete absence of vasodilator response in a patient with advanced diabetic arteriosclerosis with gangrene (case 21).

made in another hospital. In spite of dietary treatment and the use of insulin, it became necessary to amputate the second toe of the right foot. At this time there was clinical evidence that the circulation was also deficient in the third and fourth toes of the right foot.

At the time of the patient's admission to the University Hospital the temperature, pulse and respiration were normal. The blood pressure was 130 systolic and 75 diastolic. The peripheral arteries, as well as the retinal vessels, were moderately sclerosed. The tips of the third and fourth toes of the right foot presented small areas of gangrene. A few drops of purulent exudate could be expressed from the site of the previous amputation. The pulsation of the dorsalis pedis artery was felt in both feet; the posterior tibial artery was not felt on either side.

On admission the blood sugar during fasting was 189 mg. per hundred cubic centimeters, and glycosuria occurred only occasionally. Roentgen examination of the right foot revealed marked osteoporosis of the bones of the anterior part of the foot and some calcification of the arteries.

In the hospital the diabetes was controlled easily by a suitable dietary regimen with the administration of 10 units of insulin per day. The lesions of the right foot improved temporarily under conservative treatment by débridement, antiseptics and external heat.

TABLE 3.—*Vasodilator Responses in Patients with Arteriosclerosis With and Without Diabetes*

Case	Sex	Age	Side	Pain	Coldness	Cyanosis	Ulcers or Gangrene	Arterial Pulse			Room Temper- ature, C.	Toes Observed	Vasodilator Response		
								Posterior Tibial	Dorsalis Pedis	Time From Immersion to Begin- ning of Rise, Minutes			Initial Tempera- ture of Toes, C.	Time to Reach 32 C., Minutes	Temper- ature at End of Period of Immer- sion, C.
(a) Patients without Diabetes															
13	M	53	R	+	+	None	None	Not palpable	Palpable	24.0	R 1 R 3	24.1 24.0	17 18	..	31.8 29.4
			L	++	++	++++	None	Not palpable	Not palpable		L 1 L 3	26.2 24.9	6 18	..	29.5 27.1
11	M	53	R	++++	++++	++++	Ulcer	Not palpable	Not palpable	18.5	R 1 R 3	22.9 22.3	..	..	23.1 22.3
			L	None	None	None	None	Not palpable	Not palpable		L 1 L 3	23.3 23.0	7 10	..	26.9 25.4
15*	M	71	R	None	.....	.....	None	Not palpable	Not palpable	21.0	R 1	23.8	16	..	29.6
			L	+++	.....	.....	Ulcer	Not palpable	Not palpable	16.0	L 1	26.2	15	..	27.9
16*	M	63	R	++	+++	.....	Ulcer	Not palpable	Not palpable		R 1 R 3	19.6 18.8	25 25	..	21.2 20.6
			L	++	None	.....	None	Not palpable	Not palpable		L 1 L 3	17.5 17.5	17 19	..	30.5 25.6
17	M	53	R	+++	+++	++++	Ulcers	Palpable	Faintly palpable	23.5	R 1 R 3	26.5 25.6	..	..	25.5 24.7
			L	None	+++	None	None	Palpable	Faintly palpable		L 1 L 3	26.9 25.6	9 9	15 21	35.0 34.7

18	M	59	R	+++	+++	None	None	Not palpable	Not palpable	20.2	R1 R3 R5 L1 L3	21.8 21.5 22.0 21.7 21.7	.. .. .. .. ..	.. .. .. .. ..	21.8 21.4 21.7 21.1 21.4
(b) Patients with Diabetes															
19	F	24	R	None	++++	None	None	Palpable	Palpable	23.5	R1 R3	27.1 26.2	9 9	11 13	35.7 34.9
			L	None	++++	None	None	Palpable	Palpable		L1 L3	25.6 24.8	11 12	28 29	34.1 34.3
20	M	56	R	None	+++	+++	None	Palpable	Not palpable	20.0	R1 R2	19.2 19.2	.. ..	.. ..	19.9 19.8
			L	None	+++	+	None	Palpable	Palpable		L1 L2	19.0 19.2	.. ..	.. ..	19.3 19.8
										20.0	R1 R3 R5	21.9 22.4 22.9	.. .. ..	.. .. ..	21.2 21.3 21.7
											L1 L3	21.6 20.8	.. ..	.. ..	20.8 20.2
21	M	46	R	+++	++	+++	Gangrene	Not palpable	Faintly palpable	17.0	R1 R4	27.2 26.8	.. ..	.. ..	24.3 24.9
			L	None	++	+++	Threatened gangrene	Not palpable	Palpable	20.5	L1 L4 R1 R4 L1 L4	25.1 22.3 24.2 24.2 22.6 22.5	.. .. .. .. .. ..	.. .. .. .. .. ..	21.9 21.0 23.4 23.4 21.7 21.9

\* Colored patient.

On two occasions the skin temperature of the toes of both feet was measured while the forearms were immersed in warm water. The results were entirely similar, though in one instance the examination was made at a room temperature of 17 C. (62.6 F.), and in the other at 20.5 C. (68.9 F.). When the feet were exposed to the air the temperature of the toes fell slowly but constantly. Immersion of the forearms in warm water had no effect on the temperature of the toes, although subjective warmth and sweating occurred within eight minutes after warming the arms. These findings indicated the presence of a high grade of organic obstruction to circulation in the toes of both feet.

In table 3 *b* the results obtained in this patient and in two others with diabetes are summarized. One of these (case 19) was a young woman, aged 24, who had severe diabetes and who suffered only from

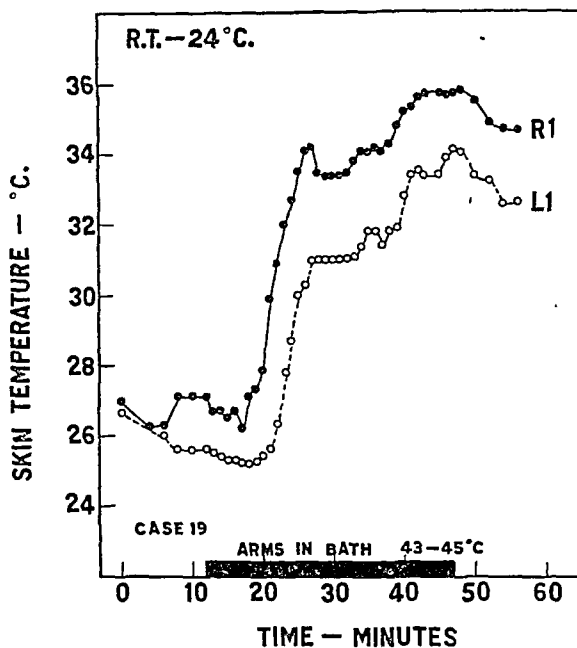


Fig. 6.—Vasodilator response in a diabetic patient (case 19) with mild symptoms of diminished circulation in the lower extremities. The response was normal in both lower extremities, indicating that the symptoms were due to vasospasm, not to organic occlusion.

coldness of the extremities without other evidence of restricted flow of blood. She had a practically normal vasodilator response (fig. 6). The other two patients (cases 20 and 21) had more severe vascular involvement with clinical evidence of organic obstruction; they showed no vasodilator response in the lower extremities when the forearms were immersed in warm water.

4. *Comparison with Other Methods of Producing Maximal Vasodilatation.*—Evidence has already been reported by us<sup>1</sup> to show that in normal subjects adequate warming of the forearms causes the skin temperature of the toes to rise above 31.5 C. (88.7 F.), the figure

adopted by Morton and Scott as the minimal normal response to general and spinal anesthesia. In eight of the thirteen patients with thromboangiitis obliterans or arteriosclerosis in whom the temperature of the toes failed to rise to the normal level on warming the forearms, some other method of producing vasodilatation was also employed.

The vasomotor index<sup>6</sup> was determined in four patients (cases 8, 9, 10 and 11) with essential agreement between the two methods used. In patient 8 the vessels of the left foot were able to dilate fully and the vasomotor index was 3.3, while in the right foot, the vessels of which failed to show normal dilatation to heat, the vasomotor index was 2.5. In patient 9 the vasomotor index for both lower extremities was zero, and the vessels failed also to show measurable dilatation when the forearms were warmed. Warming the forearms of patient 10 produced practically no vasodilator response on the left side; the vasomotor index was zero. A partial response was produced on the right side; the vasomotor index was 1.5. Patient 11 showed almost no response to warming in the right foot; the vasomotor index was 1.3. There was a much delayed response in the left foot, with a vasomotor index of 1.1. In these four patients the agreement between the vasodilator response due to warming the forearms and that due to fever was good. It is difficult to compare quantitatively methods which differ as much as these two, but the clinical interpretation of the findings was essentially the same in each case.

One patient (case 14) was studied by means of both spinal anesthesia and warming the forearms. The clinical record and the details of both examinations have been given in full by us.<sup>1</sup> The two methods of inducing dilatation were carried out at the same room temperature, and the final skin temperatures were almost identical.

Anesthetization of the posterior tibial nerve was used in three patients who showed no vasodilator response to warming the forearms. In patient 18, at a room temperature of 20 C. (68 F.), both feet were cold, the temperatures ranging from 21.5 to 22.6 C. (from 70.7 to 72.7 F.). Immersion of both forearms in warm water (43 to 45 C.) for thirty-five minutes produced no rise in the temperature of the toes. The heating was adequate since the patient felt uncomfortably warm and perspired profusely during the test (table 3). Ten days later, at a similar room temperature 3 cc. of a 2 per cent solution of procaine hydrochloride was injected around the right posterior tibial nerve. The right first and fourth toes, the temperatures of which were originally 20 and 20.7 C. (68 and 69.3 F.), became warmer as anesthesia appeared, and nineteen minutes after anesthesia was complete

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6. Brown, G. E.: The Treatment of Peripheral Vascular Disturbances of the Extremities, *J. A. M. A.* **87**:379 (Aug. 7) 1926.

the temperatures were 27.1 and 29.7 C. (80.8 and 85.4 F.) respectively. The rise in temperature was slow and incomplete, indicating a moderate grade of organic obstruction to the flow of blood. Had it been assumed in this case that complete absence of the vasodilator response to immersing the forearms in warm water was always due entirely to organic obstruction, it would have been concluded erroneously that a very high grade of obstruction was present, whereas anesthetization of the posterior tibial nerve showed that the organic obliteration was only moderate.

In two other cases the vasodilator response to heat was absent and anesthetization of the posterior tibial nerve under similar environmental conditions likewise failed to produce any rise in skin temperature. One patient (case 21) suffered from diabetes with gangrene, and the vasodilator response to warming the forearms was not obtained in two examinations at room temperatures of 17 and 20.5 C. (table 3). At a room temperature of 18 C., the injection of 3 cc. of a 2 per cent solution of procaine hydrochloride near the left posterior tibial nerve failed to produce any rise of temperature in the area of anesthesia, though the color of the skin improved slightly. The other patient (case 20) on two occasions, at a room temperature of 20 C., showed no vasodilator response to warming the forearms. Likewise, at a room temperature of 19 C., anesthetizing the right posterior tibial nerve with procaine hydrochloride failed to produce any rise in skin temperature.

Therefore, in seven of eight patients with organic vascular obstruction the results obtained by testing the reaction to warming the forearms agreed with those obtained by other methods of examination. In one patient the vasodilator response to heat failed to appear, although the vessels were shown by anesthetization of the posterior tibial nerve to be capable of limited dilatation.

5. *The Vasodilator Response in Acrocyanosis.*—According to Lewis and Landis,<sup>7</sup> the essential vascular abnormality in acrocyanosis appears to consist of heightened tone in the arterioles of the skin of the affected part at ordinary environmental temperatures. The vasodilator response to warming the forearms was tested in three patients with typical acrocyanosis involving the lower extremities. These patients had no local symptoms other than coldness of the extremities and occasional tingling in the digits. They had not suffered from ulcers, phlebitis or trophic changes.

On examination the pulsation of the posterior tibial and the dorsalis pedis arteries was felt in all these patients. The feet and hands, which

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7. Lewis, T., and Landis, E. M.: Observations upon the Vascular Mechanism in Acrocyanosis, *Heart* 15:229, 1930.

were rather more deeply red than normally when warm, cooled rapidly and became cyanotic when exposed to an air temperature of about 20 C. The discoloration was not uniform, being deeper blue in some areas, particularly over the knuckles, and more reddish in other areas. The cyanosis involved all the digits, extending in the hands to a point slightly above the wrist, and in the feet to the ankles, though it was less intense in the more proximal areas of skin. In two patients cyanosis was noted in the legs above the ankle.

The cyanosis disappeared when the extremities became warm spontaneously or as a result of immersion in warm water. With the

TABLE 4.—*Vasodilator Responses in Patients with Acrocyanosis of the Lower Extremities*

Case	Sex	Age	Room Temperature, C.	Side	Toes Observed	Initial Temperature of Toes, C.	Vasodilator Response to Warming the Forearms	Vasodilator Response to Anesthetization of the Posterior Tibial Nerve
22	M	38	19-20	R	R 1	23.1	None	Normal
					R 2	22.1	None	Normal
				L	L 1	23.4	Normal	.....
					L 2	23.2	Normal	.....
23	M	14	19-20	R	R 1	19.9	Partial and delayed	Normal
					R 3	19.8	None	Normal
				L	L 1	20.0	Partial and delayed	.....
					L 3	19.6	Partial and delayed	.....
24	M	19	18-20	R	R 1	20.4	None	.....
					R 3	20.3	None	.....
				L	L 1	20.6	None	Normal
					L 3	19.6	None	Normal

change in tint the depth of color lessened. The introduction of histamine by needle prick into the cyanotic skin released vascular spasm more or less completely in the area of flare which, in some instances, appeared brilliantly hyperemic in contrast to the adjacent cyanotic skin. Wheals appeared at the usual time around the points of puncture.

Table 4 summarizes the changes in digital temperature in the lower extremities obtained by immersing the forearms in warm water and by blocking the posterior tibial nerve with a 2 per cent solution of procaine hydrochloride. Each patient was first tested in the usual manner, the forearms and hands being immersed for thirty-five minutes in water at a temperature of between 43 and 45 C. The patients felt warm and perspired freely over the face and body during the test. Nevertheless, the skin temperature of the toes failed to rise in the normal manner, the response being absent in the more involved foot of one patient, incomplete in both feet of the second patient and totally



absent in both feet of the third patient. Anesthetization of the posterior tibial nerve, however, produced vasodilatation, and the skin temperature rose eventually to 32 C. or higher in each instance, indicating that the vessels were capable of complete normal dilatation.

In figure 7 a comparison is made of the effects on skin temperature in the toes of warming the forearms and anesthetization of the posterior tibial nerve. The feet of the patient (case 24) cooled to room temperature and were deeply cyanotic (colors XII and XIII½). On the twenty-fourth minute the forearms were immersed in warm water, but the feet failed to show the usual rise in temperature. On the seventy-fourth minute the thermal junction applied to the skin of the

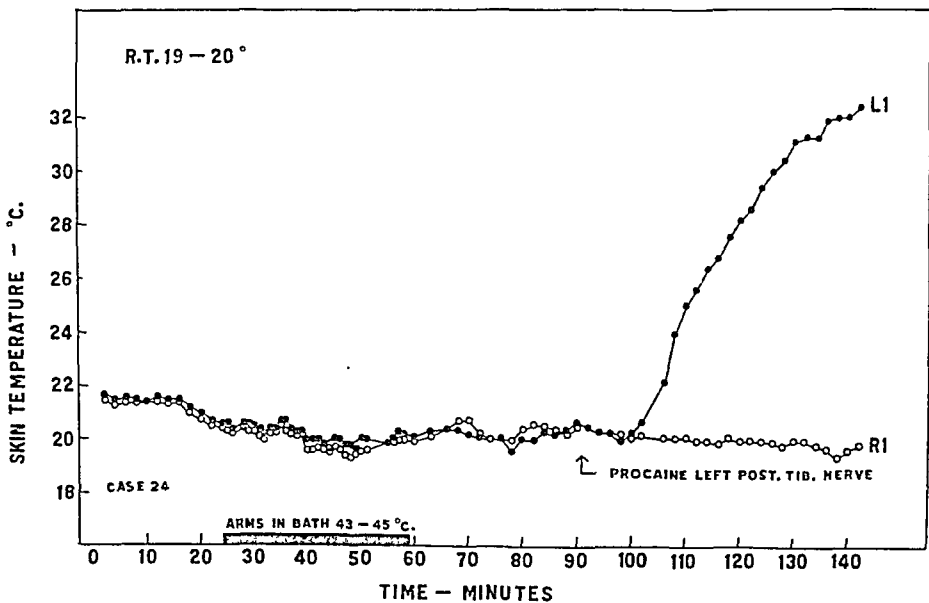


Fig. 7.—Chart showing complete absence of vasodilator response in a patient with acrocyanosis of the lower extremities (case 24) when the forearms were immersed in warm water. Injection of procaine hydrochloride around the left posterior tibial nerve produced vasodilatation and a rise in skin temperature.

left great toe was moved from the dorsal to the plantar surface to correspond with the procedure of Scott and Morton.<sup>2b</sup> On the ninety-first minute 3.5 cc. of a 2 per cent solution of procaine hydrochloride was injected in the region of the left posterior tibial nerve. Partial anesthesia appeared eleven minutes later, and nineteen minutes after the injection anesthesia was complete in the area of the nerve. It required forty minutes for the skin temperature to rise from 20 C. to 32 C., and during the last thirty minutes of this period the plantar skin of the left foot was completely anesthetic. The color of the anesthetic skin changed for the most part to a deep pink (colors VI to VII), but some areas on the plantar surfaces of the toes remained

blue (colors XII and XIII). A similar delayed, but eventually complete, response to anesthetization of the posterior tibial nerve was observed in patient 23.

#### COMMENT

The practical importance of differentiating the deficient circulation due to vasospasm from that due to organic occlusion of the arteries has been stressed sufficiently by Brown<sup>7</sup> and by Scott and Morton.<sup>2c</sup> The usefulness of sympathetic ganglionectomy in the treatment of patients with obliterative structural disease of the arteries, as indicated by Scott and Morton and by Adson and Brown,<sup>8</sup> is greatest in patients with only mild grades of organic obstruction. The best results in the treatment of peripheral vascular disease can be obtained only if the beginning organic occlusion is discovered before it has reduced too greatly the ability of the blood vessels to dilate when vasoconstrictor tone is abolished permanently by sympathetic ganglionectomy. Since early diagnosis of beginning organic occlusion will be favored by any simplification of the existing methods of examination, it was considered worth while to determine whether the vasodilator response described previously by us could be applied to the clinical study of peripheral vascular disease. Heat has been used also by Lewis and Pickering<sup>9</sup> and by de Takats,<sup>10</sup> but special apparatus is required in the methods employed by them, the body being warmed in an electric cabinet in the former case and by means of diathermy apparatus in the latter.

Vasodilatation can be produced simultaneously in both upper or in both lower limbs by immersing the other two extremities in warm water. This method is simple and requires no special apparatus except that for measuring skin temperature. The test can be performed without serious discomfort or danger to the patient, whether he is ambulatory or confined to his bed. Studies were made to determine whether this form of vasodilator response was sufficiently dependable to be recommended as a preliminary method of examination since, by reason of its simplicity, the procedure may be used by practitioners who are not equipped to apply methods such as nerve block, spinal or general anesthesia and diathermy.

The vasodilator response elicited in the lower extremities by immersing the forearms in warm water appears to be sufficiently trustworthy to use as a preliminary test of organic occlusion. In seven of eight patients

8. Adson, A. W., and Brown, G. E.: *Thrombo-Angiitis Obliterans: Results of Sympathectomy*, J. A. M. A. **99**:529 (Aug. 13) 1932.

9. Lewis, T., and Pickering, G. W.: *Vasodilatation in the Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man*, Heart **16**:33, 1931.

10. de Takats, G.: *The Differentiation of Organic and Spastic Vascular Occlusions*, Ann. Surg. **94**:321, 1931.

with thrombo-angiitis obliterans or arteriosclerosis tested by this and one other method the clinical conclusions arrived at by the two procedures were practically identical. The one exception was a patient with roentgen evidence of arteriosclerosis in the lower extremities in whom the vasodilator response to heat was completely absent while anesthetization of the posterior tibial nerve showed only a moderate grade of organic occlusion. It may be concluded that significant organic occlusion is certainly absent if the immersion of the forearms in warm water (43 to 45 C.) for thirty-five minutes causes the skin temperature of the toes to rise to 31.5 C. or more. A partial response with a rise of skin temperature in a room at 20° C. to a level below 31.5 C. indicates organic obstruction, the grade of the obstruction being roughly measured by the difference between 31.5 C. and the maximum level reached. Until more comparative studies have been made it would seem advisable to verify the conclusions based on such partial responses with some other method of examination. The test has proved extremely valuable in ruling out significant organic vascular defects in patients with mild or atypical symptoms which hardly justified the use of intravenous typhoid vaccine or of spinal or general anesthesia as a diagnostic procedure.

There are two conditions, Raynaud's disease and acrocyanosis, in which peripheral vasoconstriction due to central vasomotor tone is more or less increased by local spasm of peripheral vessels which are hypersensitive to cold. Raynaud's disease, while it may be purely a vasomotor neurosis in its earlier stages (Simpson, Brown and Adson<sup>11</sup>) is often complicated in later stages by local sensitivity of the digital and palmar arteries to cold (Lewis,<sup>3b</sup> Simpson, Brown and Adson,<sup>11</sup> and Morton and Scott<sup>2b,d</sup>). In acrocyanosis the diminished flow of blood is due apparently to spasm of the cutaneous arterioles, which are abnormally sensitive to cold (Lewis and Landis<sup>6</sup>). It is conceivable that the peripheral vascular spasm in these two conditions might prove more difficult to relax on account of the local factor which is present only rarely in thrombo-angiitis obliterans and in arteriosclerosis.

We have not had the opportunity of studying the vasodilator responses in patients showing Raynaud's malady in the lower extremities. Morton and Scott,<sup>2b,d</sup> however, observed that in some cases of Raynaud's disease, while anesthetization of the posterior tibial nerve eventually relaxes spasm in the anesthetic area, the vasodilatation is slowly progressive. Some degree of impairment in the local circulation may be noted for a considerable time after complete anesthesia is established.

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11. Simpson, S. L.; Brown, G. E., and Adson, A. W.: 'Raynaud's Disease; Evidence That It Is a Type of Vasomotor Neurosis, *Arch. Neurol. & Psychiat.* 26:687 (Oct.) 1931.

Three patients with typical acrocyanosis failed to show normal vasodilator responses during warming of the forearms. When histamine was pricked into the skin the cyanosis disappeared more or less completely in a small area corresponding to the usual flare. In these patients anesthetization of the posterior tibial nerve produced dilatation, with a concomitant increase in skin temperature to levels well above 30.5 C (86.9 F.). In the patient in whom the condition was mildest the temperature rose to the level characteristic of complete vasodilatation in a relatively short time. In the other two patients, in whom the condition was more severe, a longer time was required for the anesthesia to modify skin temperature and skin color. According to Scott and Morton,<sup>2b</sup> the maximum skin temperature is reached within from fifteen to thirty minutes after complete anesthesia is obtained, so that the delay in these patients can hardly be regarded as definitely abnormal.

Lewis and Pickering<sup>9</sup> found that warming the body in a chamber equipped with electric lamps as sources of heat produced dilatation of the vessels in the hands of patients with Raynaud's disease and acrocyanosis. This response "once initiated is rapid and of the normal type." Immersing the forearms in warm water may possibly be a slightly less adequate stimulus for producing vasodilatation in the lower extremities. Moreover, it is well known that vasoconstrictor tone is greater in the lower extremities than in the upper. Nevertheless, in earlier studies it was found that immersing the forearms in warm water at from 43 to 45 C. for thirty-five minutes produced complete vasodilatation in normal subjects at room temperatures of 11 and 16 C. (51.8 and 60.8 F.). The same procedure failed to produce complete vasodilatation in patients with acrocyanosis at room temperatures between 18 and 20 C. (between 64.4 and 68 F.). This difference is possibly due to the local sensitivity of the cutaneous arterioles to cold, rendering complete vasodilatation more difficult to obtain. Anesthesia of the appropriate mixed nerve apparently removes the spasm by primary relaxation of the deeper vessels in the arteriovenous anastomoses of the digits, the cutaneous arterioles themselves relaxing after they have become warm (Lewis and Landis<sup>6</sup>).

The anomalous results which may be obtained by warming the forearms of patients with Raynaud's disease and acrocyanosis will only rarely be confusing. The history and ordinary examination usually suffice to differentiate these vasospastic conditions from the more common peripheral vascular diseases such as thrombo-angiitis obliterans and arteriosclerosis in which it is important that the grade of organic occlusion be determined. Finally, if in a preliminary study the vasodilator response to warming the forearms is abnormal and if doubt exists with respect to the diagnosis, another method of producing vasodilatation should be used for comparison.

## SUMMARY

1. The forearms of patients were immersed in warm water (43 to 45 C.) for thirty-five minutes in order to produce vasodilatation in the lower extremities. This vasodilator response was studied in twenty-four patients who showed clinical evidence of peripheral vascular disease.

2. In seven patients with pain, coldness or cyanosis of the lower extremities the temperature of the toes rose to levels above 32 C. This normal response definitely excluded the possibility of obliterative structural disease of the arteries as a cause of the diminished flow of blood in the lower extremities.

3. Fourteen patients with thrombo-angiitis obliterans or arteriosclerosis involving the lower extremities showed varying grades of organic occlusion and spasm when tested by this method.

4. In eight of the thirteen patients who failed to show the normal vasodilator response to warming the forearms the results were compared with those obtained by some other method of producing vasodilatation, including the intravenous injection of typhoid vaccine, the use of spinal anesthesia and anesthetization of the posterior tibial nerve. In seven of the eight patients the clinical interpretation of the findings by both methods was the same. In one patient with arteriosclerosis warming the forearms failed to produce a vasodilator response, whereas anesthetization of the posterior tibial nerve showed that the vessels were capable of limited dilatation.

5. Three patients with acrocyanosis of the lower extremities showed abnormal vasodilator responses to warming the forearms, though anesthetization of the posterior tibial nerve produced complete, but rather delayed, elevations in skin temperature. These findings are discussed with reference to the mechanism of the diminished flow of blood in acrocyanosis.

6. Warming the forearms in water at a temperature of from 43 to 45 C. for thirty-five minutes is a simple and entirely unobjectionable method of producing vasodilatation in the lower extremities. If the surface temperature of the toes rises above 31.5 C., significant obliterative structural disease of the arteries of the lower extremity is definitely absent. If the surface temperature fails to rise to this level, organic arterial obstruction is probably present. With controlled room temperature, the approximate grade of the organic obstruction is indicated by the difference between 31.5 C. and the maximum temperature reached. For absolute certainty in the diagnosis of organic arterial obstruction the abnormal vasodilator responses obtained by warming the forearms should be confirmed by some other method of producing peripheral vasodilatation.

# EFFECT OF ALKALI ON THE ABSORPTION OF THYROXINE FROM THE GASTRO- INTESTINAL TRACT

WITH A NOTE ON THE COMPARATIVE EFFECTS OF SYNTHETIC AND  
"NATURAL" THYROXINE INJECTED INTRAVENOUSLY

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We have just reported observations which show that when thyroxine is administered by mouth in the form of its monosodium salt to patients with myxedema it has only about from one-third to one-fifth as much effect as when it is administered intravenously in alkaline solution (sodium hydroxide).<sup>1</sup> This conclusion was based on the amounts of the two substances which had to be administered every day in order to hold the basal metabolism at the normal level. Pure thyroxine had much less effect than its monosodium salt. Since when thyroxine is dissolved in an excess of sodium hydroxide the disodium salt is presumably formed, it seemed logical to try the effect of administering the hormone by mouth in an alkaline solution.

Klein<sup>2</sup> reported that Hoffmann-La Roche thyroxine solution for oral use, Schering thyroxine in alkaline solution with the same  $p_H$  as

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1. Thompson, W. O.; Thompson, P. K., and Dickie, L. F. N.: Monosodium Thyroxine, Desiccated Thyroid and an Impure Sodium Salt of Thyroxine: Comparison of Their Effects When Administered Orally with the Effect of Thyroxine Injected Intravenously in an Alkaline Solution, Arch. Int. Med. **52**:576 (Oct.) 1933.

2. Klein, B.: Ueber die hohe Wirksamkeit peroral verabreichten Thyroxin-natriums bei normalen und hypothyreotischen Individuen, Ztschr. f. klin. Med. **119**:477, 1932.

the Hoffmann-La Roche solution and Schering's *Trinktabletten* all have a greater effect on the basal metabolism than the tablets which the Schering Corporation ordinarily sells for oral use. The two solutions and the *Trinktabletten* are said to contain dialkali salts of thyroxine, whereas the Schering tablets commonly sold for oral administration presumably contain the monosodium salt of thyroxine. Baur and Loewe<sup>3</sup> stated that an alkaline solution is more effective than tablets (presumably monosodium salt), especially if the alkaline solution is markedly diluted. The data on this point are very meager, and we know of no observations in which the effects of administering thyroxine in alkaline solution by the oral and parenteral routes have been compared in the same patient.

#### METHOD

In this study we have used as a basis of comparison the effect of a single dose of the substance concerned on the basal metabolism. Only patients with definite myxedema were used because in them the effect of thyroxine on the basal metabolism is greater than in normal persons. There were three such patients. In the first and second the myxedema was spontaneous, and in the third it followed a subtotal thyroidectomy for exophthalmic goiter.

For all intravenous injections the thyroxine was prepared by dissolving it in a few cubic centimeters of distilled water by the addition of from 1 to 3 drops of 10 per cent sodium hydroxide. The solution was sterilized on a water bath for the first patient and for the second injection in the second patient. For the other injections it was sterilized by the addition of 1 cc. of 1:1,000 merthiolate<sup>4</sup> to make a dilution of 1:5,000. For oral administration of an alkaline solution the method varied slightly, as described in the legends. Sodium bicarbonate was always administered with the alkaline solution. All thyroxine administered by mouth was synthetic thyroxine (Hoffmann-La Roche) or one of its sodium salts. The monosodium salt was administered in the form of tablets prepared by Hoffmann-La Roche, each of which contained 1.03 mg. of the salt, or the equivalent of 1 mg. of pure thyroxine.

Basal metabolic rates were determined by means of the Sanborn-Benedict apparatus, with the Aub-DuBois standards.

The data on the second patient up to the forty-second day and those on the third patient up to the one hundred and forty-fourth day have been reported elsewhere to illustrate another point.<sup>5</sup>

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3. Baur, H., and Loewe, G.: Ueber die Wirkung des synthetischen Thyroxins beim Menschen mit normaler Schilddrüse, *Deutsches Arch f. klin. Med.* **159**:275, 1928.

4. One gram of sodium ethylmercuri-thiosalicylate in 1,000 cc. of water buffered with 1.4 Gm. of sodium borate in 1,000 cc. and containing sodium chloride to make the solution approximately isotonic. This preparation was supplied by the manufacturers, Eli Lilly and Company, Indianapolis.

5. Thompson, W. O.; Alper, J. M.; Thompson, P. K., and Dickie, L. F. N.: The Effect of Diiodotyrosine on the Basal Metabolism in Myxedema, to be published in the *Journal of Clinical Investigation*, January, 1934.

## DATA

The data are recorded in charts 1 to 6 and summarized in the table.

The excess basal calories produced by the various doses of thyroxine were calculated as in a previous communication by Thompson, Thompson, Brailey and Cohen.<sup>6</sup> The daily metabolic rates were plotted on graph paper (charts 4 to 6) ruled in small squares (sample insert in each chart), each small square representing a change of 1 per cent in the normal basal calories per square meter for twenty-four hours. A curve was then plotted to denote the course of the metabolism. The base line was the level of the metabolism before the administration of

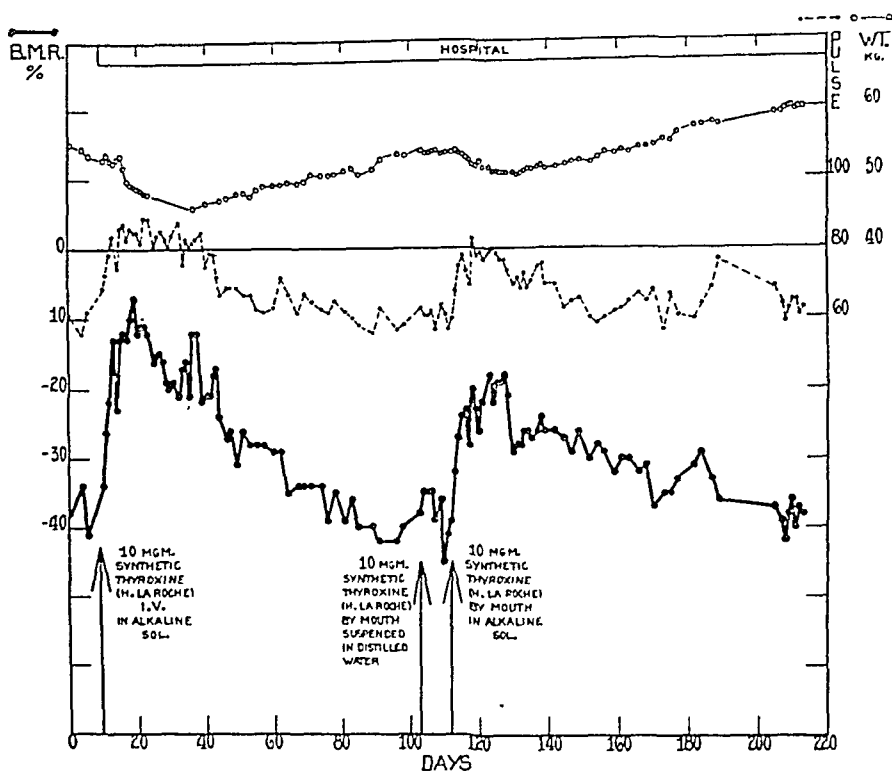


Chart 1.—Comparison of effects of an alkaline solution of thyroxine administered orally and intravenously and of pure thyroxine administered by mouth in a patient with myxedema (Mrs. M. M., height 159 cm., age 58). Intravenous injection at 10:10 p. m., Oct. 8, 1932. The oral dose of pure thyroxine was administered without breakfast or lunch at 12:30 p. m., Jan. 10, 1933, suspended in distilled water, a total of 200 cc. being used, largely for rinsing. The oral dose of thyroxine in alkaline solution was given without breakfast at 10:31 a. m., January 19, 2 drops of 10 per cent sodium hydroxide, and a total of 100 cc. distilled water being used for solution and rinsing. A total of 70 grains of sodium bicarbonate and 350 cc. of distilled water was also administered in six doses from 10:30 a. m. to 11:30 a. m., a single dose of 15 grains being given just before the thyroxine. In this and subsequent charts, the arrows denote the time of administration of thyroxine and *I.V.*, an intravenous injection.

6. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: The Calorigenic Action of Thyroxin at Different Levels of Basal Metabolism in Myxedema, *J. Clin. Investigation* 7:437, 1929.



thyroxine. The number of squares contained in the area bounded by the base line and the curve was counted. The difference in the number of squares in the graphs for the various methods of administering thyroxine gives a fairly close estimate of the difference in the magnitude of the response to each: but to bring each response to terms of total excess heat production, the normal basal metabolic rate in calories for twenty-four hours was multiplied by the number of squares and the result divided by one hundred. In each calculation the figure used for surface area is that of the patient just before the administration of thyroxine. The ensuing changes in area are not taken into account

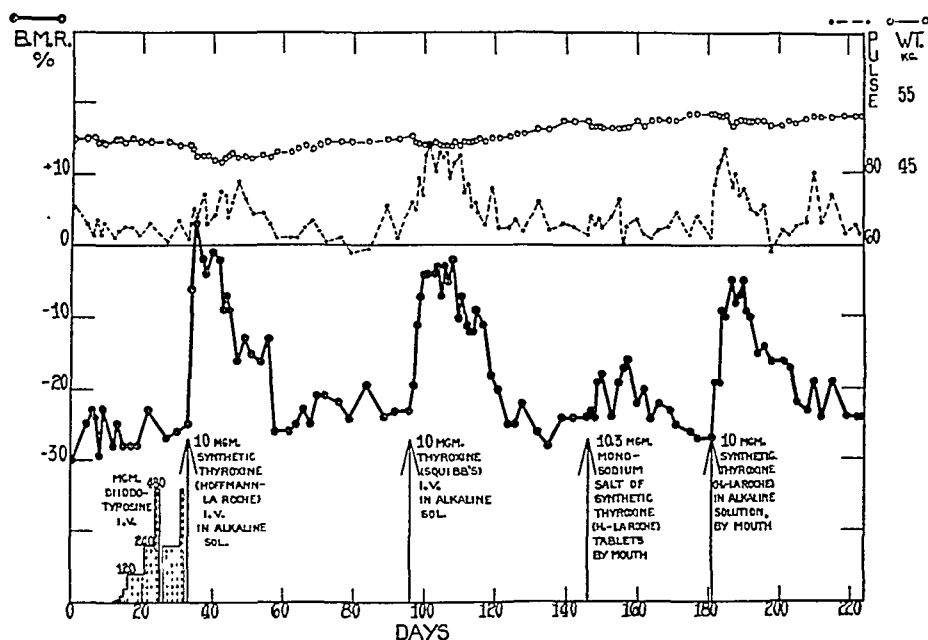


Chart 2.—Comparison of effects of administering an alkaline solution of thyroxine orally and intravenously and monosodium thyroxine by mouth in a patient with myxedema (Mrs. M. K., height 152 cm., age 36). The effects of administering synthetic and natural (Squibb's) thyroxine intravenously are also compared. The intravenous injection of synthetic thyroxine was made about 11:30 a. m., Aug. 8, 1932 (without breakfast), and the intravenous injection of the Squibb's thyroxine at 4:30 p. m., October 10. The monosodium salt was administered with about 100 cc. distilled water at 3:30 p. m., November 29 (she had had dinner at 12:15 p. m.). The thyroxine in alkaline solution (30 cc., with 3 drops of 10 per cent sodium hydroxide) was administered at 3:53 p. m., Jan. 3, 1933, after a mid-day dinner. A total of 50 grains of sodium bicarbonate with 165 cc. of distilled water was also given in five equal doses, from 3:51 to 5:15 p. m., the first dose being given just before the administration of the thyroxine.

because the influence on final results is so slight. As pointed out in the communication referred to, this method of calculating excess calories

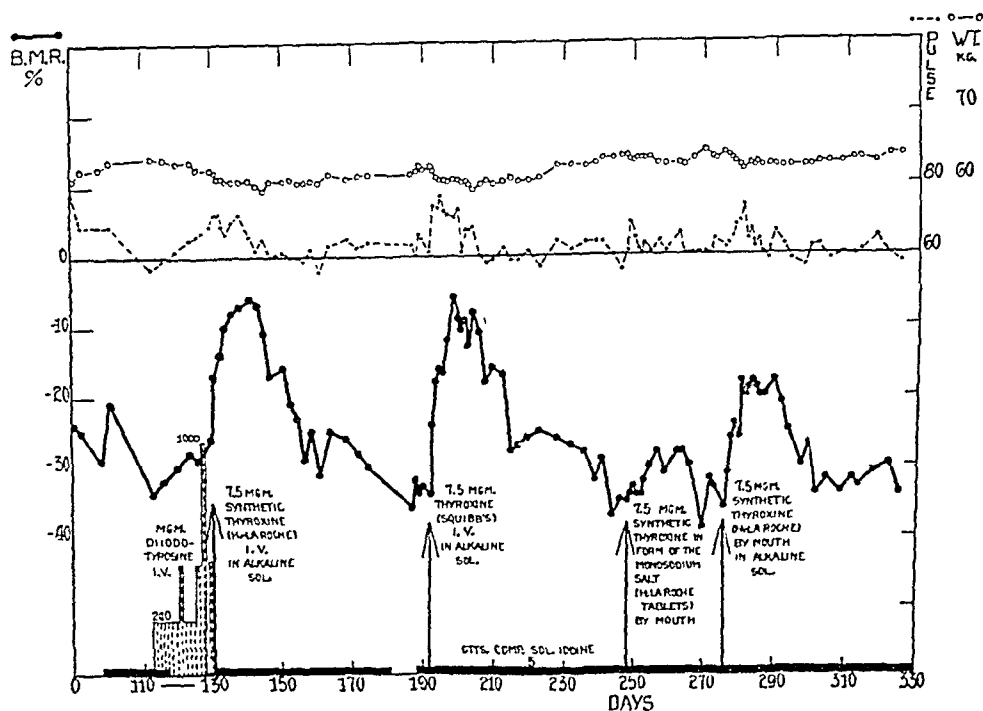


Chart 3.—Comparison of effects of administration of an alkaline solution of thyroxine orally and intravenously and monosodium thyroxine by mouth, and a comparison of the effects of administering synthetic and natural thyroxine intravenously, in a patient with myxedema (Mrs. A. R., height 160 cm., age 33). The intravenous injection of synthetic thyroxine was made about 11:30 a. m., Aug. 16, 1932, and the intravenous injection of natural (Squibb's) thyroxine at 3:30 p. m., October 17, after lunch. The monosodium thyroxine was given, without breakfast, at 11:30 a. m., December 12, with about 125 cc. of distilled water. The oral administration of synthetic thyroxine in alkaline solution (30 cc., with 4 drops of 10 per cent sodium hydroxide) was made at 2:48 p. m., Jan. 9, 1933 (the patient did not have breakfast or lunch). In addition, 60 grains of sodium bicarbonate was administered with 160 cc. distilled water in six equal doses, from 2:47 p. m. to 4:15 p. m., only one dose being given before the thyroxine. The solid black area represents the administration of compound solution of iodine.

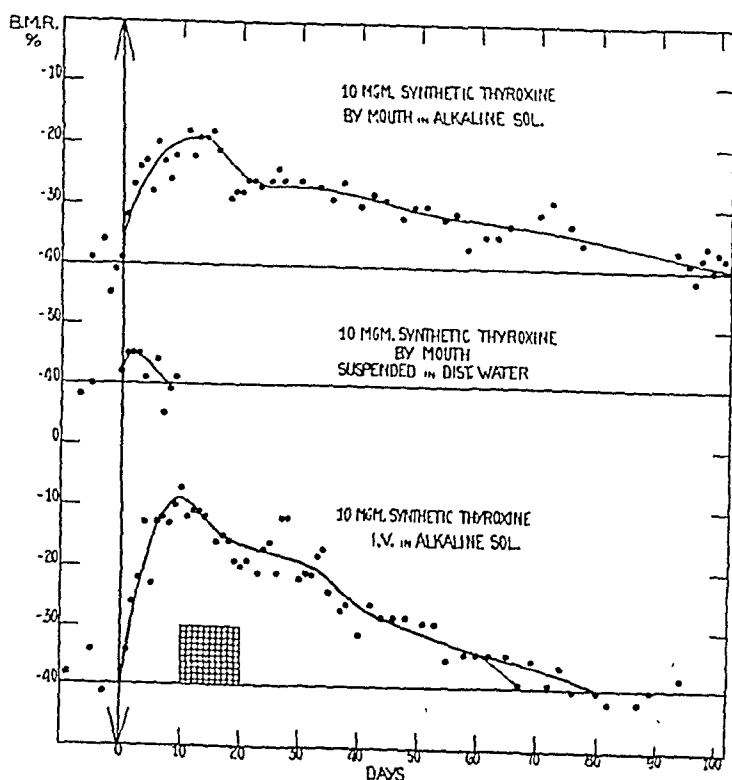


Chart 4.—Detailed comparison of effects on basal metabolism of various administrations of 10 mg. of thyroxine in the first patient.

is only a rough one because the number of calories produced above the basal value undoubtedly varies with different metabolic levels.

It may be seen that thyroxine in alkaline solution had from 68 to 80 per cent as much effect by mouth as by intravenous injection in terms of the amount of increase in the metabolism, and about 72 to 84 per cent as much effect in terms of total excess calory production. It may

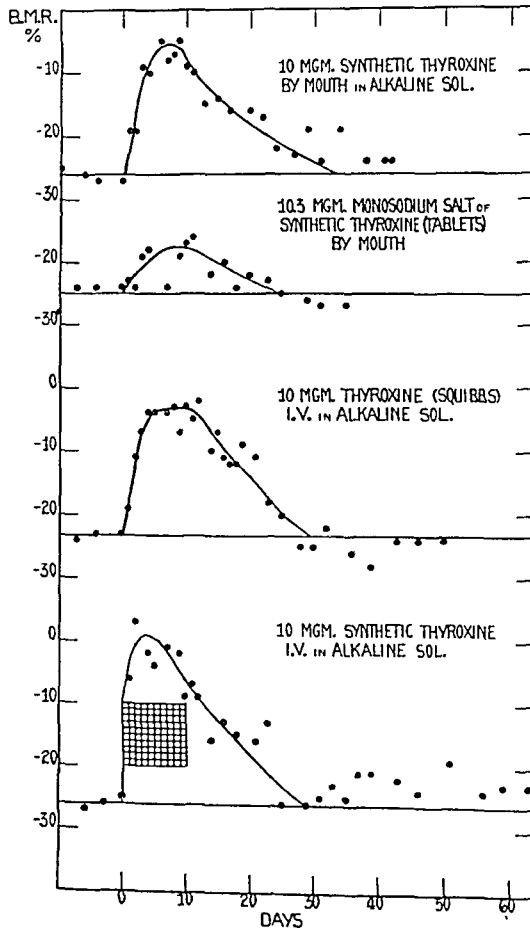


Chart 5.—Detailed comparison of effects on basal metabolism of various administrations of 10 mg. of thyroxine in the second patient. The 10.3 mg. of monosodium thyroxine is equivalent to 10 mg. of thyroxine.

also be noted that in the first patient the oral administration of 10 mg. of pure synthetic thyroxine in a single dose was without a clearly demonstrable effect on the basal metabolism. In the second and third patients, single doses of 10 and 7.5 mg., respectively, of synthetic thyroxine in the form of the monosodium salt produced increases in total excess calories only about one-third and two-fifths as great, respec-

tively, as the same doses by mouth in alkaline solution. In making these comparisons, only the results with synthetic thyroxine have been used.

In the first patient there was a normal amount of hydrochloric acid in the gastric contents after a test meal. In the second patient the amount of free and combined acid was small, both with and without histamine. The third patient showed no free acid and low total acidity before and after a test meal.

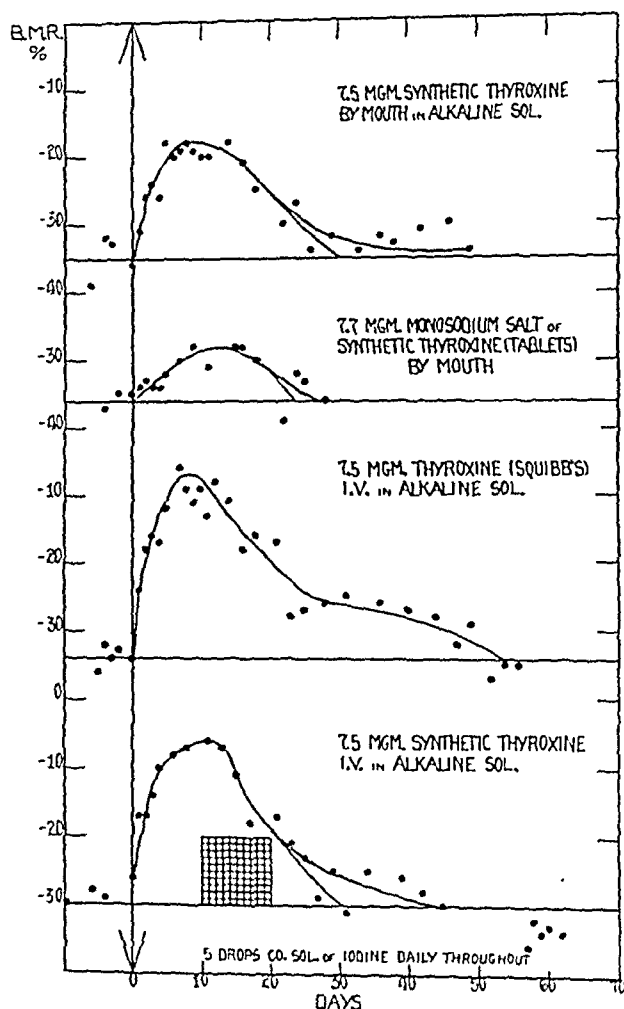


Chart 6.—Detailed comparison of effects on basal metabolism of various administrations of 7.5 mg. of thyroxine in the third patient. The 7.7 mg. of monosodium thyroxine is equivalent to 7.5 mg. of thyroxine.

We believe that the extra alkali given as sodium bicarbonate probably had no effect on the final results because of effects recently obtained by administering 10 mg. of thyroxine by mouth in alkaline solution to three patients in the same manner as to the patients of this study, except that no sodium bicarbonate was given. In the first the basal metabolism rose from minus 34 to minus 10 per cent, in the second from minus 22 to minus 7 per cent, and in the third from minus 39 to minus 18 per cent.

*Summary of Effects of Various Methods of Administration of Thyroxine on the Basal Metabolism and Excess Calory Production in Three Patients with Myxedema*

Patient	Medication	Basal Metabolism Before Administration, % Normal	Level to Which Basal Metabolism Rose, % Normal	Surface Area Before Injection, Sq. M.	Number of Squares	Total Excess Calories	Excess Calories per Square Meter Body Surface	Per Cent of Rise in Basal Metabolism per Mg. Administered	Time Required for Basal Metabolism to Rise to Maximum, Days	Total Length of Time Basal Metabolism Affected, Days
1	10 mg. synthetic thyroxine intravenously in alkaline solution .....	-40	-11	1.52	1,150	14,860	9,775	2.9	9	80
	10 mg. synthetic thyroxine by mouth suspended in distilled water .....	-40	-35	1.52	24	310	205	0.5	1	8
	10 mg. synthetic thyroxine by mouth in alkaline solution .....	-40	-19	1.53	958	12,050	7,875	2.1	6	95
2	10 mg. synthetic thyroxine intravenously in alkaline solution .....	-26	-1	1.42	408	5,135	3,615	2.5	2	29
	10.3 mg. natural thyroxine (Squibb's) intravenously in alkaline solution .....	-23	-4	1.44	342	4,200	2,985	1.9	4	29
	10.3 mg. monosodium salt of synthetic thyroxine (tablets) by mouth .....	-25	-19	1.46	102	1,305	895	0.6	3	25
	10 mg. synthetic thyroxine by mouth in alkaline solution .....	-26	-6	1.47	332	4,315	2,935	2.0	6	33
3	7.5 mg. synthetic thyroxine intravenously in alkaline solution .....	-30	-7	1.63	476	6,910	4,240	3.1	6	45
	7.5 mg. natural thyroxine (Squibb's) intravenously in alkaline solution .....	-31	-9	1.63	623	9,000	5,520	3.3	7	53
	7.7 mg. monosodium salt of synthetic thyroxine (tablets) by mouth .....	-36	-29	1.65	125	1,825	1,105	0.9	6	27
	7.5 mg. synthetic thyroxine by mouth in alkaline solution .....	-35	-19	1.65	342	4,990	3,025	2.1	5	42

## COMPARISON OF EFFECTS OF SYNTHETIC AND "NATURAL" (SQUIBB'S) THYROXINE

Although the effects of synthetic thyroxine and thyroxine as isolated from the thyroid gland have been compared by several observers in different ways, few comparisons have been made in patients with myxedema, and about a year ago it became necessary for us to be doubly sure that these two substances were the same. Our data are recorded with those on the second and third patients. It may be seen that there are slight variations, which may be largely the result of slight variations in the levels of metabolism when the injections were given. The effect of synthetic thyroxine was slightly greater in the second patient and slightly less in the third, but the total change in basal metabolism and the total number of excess calories in each patient agree about as closely as might be expected in measurements of this sort. Similar curves have been reported by Møller, Gram and Schou.<sup>7</sup>

## COMMENT

We<sup>8</sup> have just observed that in a patient with marked myxedema the basal metabolism which was minus 40 per cent before treatment could be maintained at the normal level by the prolonged daily oral administration of about 50 mg. of pure thyroxine suspended in distilled water. We have previously shown<sup>9</sup> that it is necessary to administer from 0.3 to 0.35 mg. of thyroxine intravenously every day to patients with marked myxedema to hold the basal metabolism at the normal level. Since the effect of thyroxine in alkaline solution by mouth is not less than one half of its effect intravenously, it would probably not be necessary to administer more than from 0.6 to 0.7 mg. in this form by mouth every day to hold the basal metabolism of a thyroidless person at the normal level. Although final figures have not yet been obtained for pure thyroxine, it would appear that, by the oral route, it is not more than one seventy-fifth as effective as its disodium salt, and that the monosodium salt is only about from one-third to two-fifths as effective. Pure thyroxine by mouth probably has not more than one-hundred-and-fiftieth as much effect as thyroxine given intravenously in alkaline solution. The reason for the slightly lesser

7. Møller, E.; Gram, C. N. J., and Schou, S. A.: Quantitative Clinical and Spectrophotometrical Comparison Between Natural and Synthetic Thyroxine, *Acta med. Scandinav.* **74**:85, 1930.

8. Thompson, W. O.; Taylor, S. G., III; Thompson, P. K., and Dickie, L. F. N.: Unpublished data, 1933.

9. Thompson, W. O.; McLellan, L. L.; Thompson, P. K., and Dickie, L. F. N.: The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man: The Relation Between the Iodine in Desiccated Thyroid and in Thyroxine, *J. Clin. Investigation* **12**:235, 1933.

effect of thyroxine in alkaline solution by the oral than by the intravenous route is not certain. A small amount may be destroyed in the gastro-intestinal tract or fail to be absorbed.

Our observations, together with those of Klein<sup>2</sup> and Baur and Loewe,<sup>3</sup> would seem to clear up much of the mystery about the supposed lack of absorption of thyroxine from the gastro-intestinal tract. Pure thyroxine is very insoluble in water and most organic solvents; the mono-alkali salts are slightly soluble in water, and the dialkali salts are easily soluble to the extent of about 4 per cent (Kendall<sup>10</sup>). When desiccated thyroid is given by mouth, digestion in the stomach and small intestine presumably results in the liberation of thyroxine in peptide combination and possibly of some free thyroxine. According to Harrington and Salter,<sup>11</sup> thyroxine in peptide combination has a wide range of solubility. Salter, Lerman and Means<sup>12</sup> reported thyroxine polypeptide to be only slightly less active by mouth than thyroxine of the same iodine content given intravenously. We have recently noted that a peptide of thyroxine which Dr. S. Nadler prepared by the method of Harrington and Salter was insoluble in distilled water but soluble in an excess of sodium hydroxide. When administered by mouth suspended in distilled water our peptide produced about the same effect as the monosodium salt of thyroxine, whereas, when administered by mouth in alkaline solution, its effect was slightly greater than that of thyroxine in alkaline solution. The most important factor in the absorption of thyroxine from the gastro-intestinal tract would, therefore, appear to be the solubility of the compound administered. Salter, Lerman and Means<sup>12</sup> reported an increase in metabolism from about minus 37 per cent to about minus 8 per cent following the single oral administration of 13 mg. of thyroxine polypeptide containing 6.5 mg. of iodine, which is the amount contained in 10 mg. of thyroxine. They also reported increases from about minus 33 per cent to about minus 10 per cent and from about minus 37 per cent to about minus 10 per cent, respectively, in two patients following single oral doses of 10 mg. of thyroxine polypeptide containing 4.9 mg. of iodine. We have noted similar changes following the oral administration of our peptide in alkaline solution. In the six patients with myxedema in whom we have observed the effect of a single oral dose of thyroxine in

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10. Kendall, E. C.: Thyroxine, New York, The Chemical Catalog Company, Inc., 1929.

11. Harrington, C. R., and Salter, W. T.: The Isolation of 1-Thyroxine from the Thyroid Gland by the Action of Proteolytic Enzymes, *Biochem. J.* **24**:456, 1930.

12. Salter, W. T.; Lerman, J., and Means, J. H.: The Calorigenic Action of Thyroxine Polypeptide, *J. Clin. Investigation* **12**:327, 1933.

alkaline solution, the increase in metabolism has been at the rate of from 15 to 24 points per 10 mg. of thyroxine. We feel that more data are necessary to prove conclusively whether or not thyroxine in alkaline solution has less effect by mouth than thyroxine polypeptide. We have just made observations which show that in different patients with myxedema a single large dose of desiccated thyroid may have either less or greater effect than a single oral dose of an alkaline solution of thyroxine of equal iodine content.

Our data clearly show that in preparing thyroxine for routine oral administration only the dialkali salt should be used. In this way it is possible to treat patients with myxedema almost as cheaply with thyroxine as with desiccated thyroid. We can now obtain tablets of the monosodium salt at a cost of 3 cents per 1.03 mg. Since the disodium salt is as easy to make as the monosodium salt, the cost should not be any greater. From the data presented it would seem that a patient with marked myxedema and a basal metabolism of minus 40 per cent would require not more than 0.65 mg. daily or about 238 mg. per year of disodium thyroxine to maintain the basal metabolism at the normal level. The yearly cost would be about \$7. The same patient would require about 1½ or 2 grains (0.097 or 0.13 Gm.) daily of desiccated thyroid, containing 0.23 per cent of iodine. Such tablets may be purchased at the rate of 39 cents per hundred for the 1 grain tablets (0.065 Gm.) or 49 cents per hundred for the 2 grain tablets. Thus the cost per year for desiccated thyroid would be about \$2. In brief, the disodium salt of the synthetic thyroxine, if used orally, would cost only about three and one-half times as much as desiccated thyroid. On the other hand, the comparatively enormous cost of using pure synthetic thyroxine by mouth may be noted. It would cost about \$1 a day or \$365 per year to maintain the basal metabolism of a thyroidless person at the normal level. If pure "natural" thyroxine were used, the cost would be about twelve and one-half times as great, or about \$4,500 per year.

Since the form in which thyroxine is administered plays such an important rôle in its absorption from the gastro-intestinal tract, it is desirable that manufacturers should state precisely what their thyroxine tablets contain. Thus, one manufacturing company, on the labels on the bottles containing monosodium thyroxine, states that each tablet contains 1 mg. of crystalline synthetic thyroxine, whereas each tablet actually contains 1.03 mg. of the monosodium salt of synthetic thyroxine. When it is recalled that the pure substance has only about one thirty-fifth as much effect as its monosodium salt, the importance of making the distinction is obvious.



## SUMMARY

In three patients with myxedema, single doses of 7.5 and 10 mg. of synthetic thyroxine in an alkaline solution had from 68 to 80 per cent as much effect on the basal metabolism when administered by mouth as when injected intravenously, in terms of the increase in basal metabolism and from about 72 to 84 per cent as much effect in terms of excess calory production.

The same doses given by mouth in the form of the monosodium salt to two patients had only from one-third to two-fifths as much effect as an alkaline solution given by mouth.

In one patient a single dose of 10 mg. of pure synthetic thyroxine by mouth produced too slight a change to be measured.

The solubility of any thyroxine compound administered appears to play an important rôle in its absorption from the gastro-intestinal tract and hence in its effect on the basal metabolism.

In two of the patients the intravenous injection of synthetic thyroxine produced approximately the same increase in basal metabolism as an equal dose of "natural" thyroxine.

## Book Reviews

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**Handbuch der allgemeinen Hämatologie.** Edited by Hans Hirschfeld, Berlin, and Anton Hittmair, Wels. Volume I. Price, 139 marks. Pp. 1,523, with 162 text figures, 43 colored plates and 4 plates in black. Berlin: Urban & Schwarzenberg, 1932-1933.

This handbook is so extensive that it will be impossible to discuss the details of any of its chapters within the limits allowed for a book review. A general survey of its contents is about all that can be attempted. Volume I has been completed, and the first half of volume II has also been published. The present discussion is concerned with the former, which is made up of a series of twenty-four monographs, five of which have been written by the editors and the remainder by other contributors, among whom there are many well known names.

As indicated by the title, this book deals with the general phases of hematology and not with the diseases of the blood as such. Many of the chapters, however, will be of great value to those whose interest is primarily in the diseases of the blood and their clinical aspects. Among these may be mentioned the sections on normal and pathologic morphology of erythrocytes (Günther), normal and pathologic physiology of erythrocytes (Denecke), normal and pathologic morphology of the leukocytes of the circulating blood (Hittmair), normal and pathologic physiology of leukocytes (Hirschfeld), blood metabolism (Bingold), blood volume (Seyderhelm), leukocytosis and leukopenia (Ernst Friedrich Müller), normal and pathologic morphology and physiology of the spleen (Wolff, Hirschfeld) and the effects of radiation on the blood and blood-forming organs (Halberstaedter and Simons).

Chemists will be interested in the extensive (pp. 99-222) and carefully written section on "Chemistry of Erythrocytes and of Hemoglobin" by Otto Schumm, Hamburg. This section contains about everything that could be included under the heading, and it is so well organized that it will appeal to readers who have only a general interest and whose chemical education may not be up to the demands of this difficult field. Among the topics considered are chemical composition of erythrocytes, hemoglobin and its relations to myochrome, myohematin and cytochrome, chemical structure of hemoglobin, globin, kathemoglobin and parahematin and hematin from plants. The different forms of porphyrin are treated in great detail.

The section on "Normal and Pathologic Morphology of Erythrocytes" by Hans Günther, Leipzig (pp. 1-98), begins with a statistical treatment of the number, volume and dimensions of erythrocytes under normal and pathologic conditions, including the effects of liver treatment on these values in pernicious anemia, and is followed by the mathematical calculations for volume and surface of erythrocytes. It is pointed out that the increase or decrease in the diameters of the red cells should be distinguished sharply from changes in volume. Thus in pernicious anemia the macrocytosis is largely an increase in average diameter (*Makroplanie*) without corresponding change in volume, while in hereditary hemolytic icterus the diminished diameter (*Mikroplanie*) is associated with an increase in volume up to 14 per cent. It is claimed that the elliptic form is the dominating one for all vertebrates, and that the degree of eccentricity shows differences that are characteristic of the species and individual. Hypereccentricity is constant in pernicious anemia but not in other conditions except the constitutional anomaly known as elliptocytosis. The remainder of the chapter is devoted to such morphologic features as Heinz bodies, basophilic stippling, Jolly's bodies and reticulation, contains a great deal of carefully analyzed information and is concluded with a discussion of endoglobular parasites.

In the chapter on "Normal and Pathologic Physiology of Erythrocytes" (pp. 223-269), G. Denecke discusses the origin, maturation and functions of these cells, together with the factors which influence their formation and delivery to the blood stream. The influence of the endocrine glands on the maturation of erythrocytes, the chemistry of respiration and the question of hemolysis as a factor in the final dissolution of the red cells are discussed in some detail.

In the section on "Normal and Pathologic Morphology of the Leukocytes of the Circulating Blood" (pp. 271-337), Anton Hittmair discusses general cell morphology, including atypical, youthful and aged forms, and the special morphology of the cells of the blood and of those that may appear in the blood in pathologic conditions. The section is illustrated with two colored plates and a large number of photomicrographs. The figures of the colored plates are mostly illustrations of different types of *Stammzellen* (stem cells) of which Hittmair recognizes a confusing number, some of which are not generally acknowledged by other hematologists. The chapter is altogether too brief, considering the territory covered, and references to the literature are often misleading. In the discussion of cell origins and relationships old terminology is often used with a new meaning which makes the chapter confusing to one who is not familiar with the literature of this field. The lymphoidocyte of Pappenheim (morphologically identical with Naegeli's myeloblast) is now a cell that shows reticulo-endothelial characteristics and is more primitive than the myeloblast. The hemocytoblast is also a more primitive cell than the cells described by Ferrata and Maximow under this same term. The blood cell-forming capacity of the undifferentiated mesenchyme of the adult is emphasized and illustrated, and it is pointed out that the undifferentiated mesenchymal cells and the different stages of their differentiation to various types of blood cells may appear in the blood in pathologic conditions. This leads the author to set up a series of histioid (reticulo-endothelial) stem cells which are inserted between the fixed stroma cell which has the capacity to form blood cells and the more highly differentiated myeloblasts, lymphoblasts and other cells. Ferrata's hemohistioblast (which Ringoen and Lambin believe is an artefact) is one of these intermediate cell types.

The "Chemistry of the Leukocytes" is discussed by Alfred Neumann, Vienna (pp. 339-380). He concludes that there is a distinct chemical difference between lymphocytes and granular leukocytes. Substances belonging to the Histon group are found only in the former, while glycogen is found only in the myeloid cells. Analogous leukocytes from different animal species show great chemical differences. Leukocyte granules are products of cell activity; they are colloidal and of complicated structure, as shown by Neumann's investigation of eosinophil granules, which were found to contain iron in variable quantity.

An interesting discussion of the physiology of leukocytes is found in the section by Hans Hirschfeld, Berlin (pp. 381-434). The following topics are considered: locomotion and motility, phagocytosis, bactericidal products from leukocytes, ferment action and metabolism. Only the leukocytes of the blood are considered, and physiologic problems other than those mentioned are left for other chapters.

The subject of "Blood and the Vegetative Nervous System" is considered in great detail by E. F. Müller, Hamburg (pp. 435-502). The discussion of the effects of nervous impulses on the distribution of the polymorphonuclear leukocytes (p. 483) is of special interest and importance.

A summary of the knowledge of blood platelets and hemokonia is given by A. Hittmair in the section dealing with these structures (pp. 501-548). The lack of figures makes the morphologic descriptions somewhat unsatisfactory. The following topics are considered: normal and pathologic morphology and physiology, embryology, origin and destruction of platelets, chemistry, counting methods, variations in number, the platelets in hemorrhagic diseases and the functions and properties of platelets.

The section on "Blood Formation in the Embryo" by William Knoll, Hamburg (pp. 553-600), is an exceedingly well written and illustrated (seven colored plates) chapter. Blood development at different embryonic periods in man and mammals

is considered in detail, and the knowledge of conditions in the lower vertebrates is summarized. It is pointed out that the primitive red cells of the first generation are identical with the megaloblasts of pernicious anemia, and that there are no transitions between these and the normoblasts of the second generation. The blood of an advanced case of pernicious anemia is much like that of the human embryo of the first month, including the large bell-shaped primitive erythrocytes. Some cases of icterus gravis neonatorum have a blood picture identical with that of the 3 or 4 month embryo. Facts like these show the practical value of studies on the blood in the embryo. Sixteen pages of bibliography complete this section.

K. Bingold, Nürnberg, has written an extremely stimulating section on *Blutstoffwechsel* (blood metabolism, pp. 601-646), based largely on his own researches. The experiments on the effects of living colonies of pneumococci on the hemoglobin of blood-agar mixtures heated to different temperatures are of special interest. The chapter attempts to answer such questions as, how does the organism dispose of blood from hematomas, which hemoglobin derivatives are encountered in the body, and can these substances be used as a measure of the rate of hemoglobin production and destruction, where does hemoglobin degradation end, and is iron metabolism an index of hemoglobin metabolism? The chapter is largely a discussion of the mechanism of hemoglobin synthesis and destruction and the changes which take place during respiration. It is one of the most lucid and interesting discussions of these topics that the reviewer has seen.

In the section on "Blood Volume" (pp. 647-734), Richard Seyderhelm (Frankfurt am Main) and Walter Lampe (Eschwege) present the details of various older and newer methods for determining blood volume, with a critical discussion of their value. They conclude that none of the methods give accurate results. The colorimetric method depending on the use of stains gives values for blood plasma only, while the carbon monoxide method determines only the mass of red corpuscles. Neither one of these methods gives correct values, but a combination of the two gives a figure for total blood volume that is sufficiently accurate to show significant changes in pathologic conditions. The influence of various physiologic (including the new-born and the infant) and pathologic states on blood volume is discussed, and there are tables to show values obtained by different methods.

The section on "Leukocytosis and Leukopenia" (pp. 735-868 and twenty-six pages of bibliography) by E. F. Müller is on a broad basis and contains much new material. General features are discussed at length, and the distinction between leukocytosis and leukopenia that are due to variations in distribution between peripheral and splanchnic vessels and the corresponding states resulting from hyperfunction or hypofunction of the marrow is emphasized. Leukocytes participate in the functions of different organs and tissues, and this is expressed by the increased retention of leukocytes in hyperactive organs. An attempt is made to correlate blood pictures with the state of the bone marrow, and the distinction between a hyperactive normal myelocytic and erythroblastic marrow and one that has undergone myeloblastic transformation is stressed. Clinical applications and diagnostic values are included in the discussion which represents a valuable contribution to this field.

F. J. Lang's (Innsbruck) section (pp. 895-941) is concerned with the mechanism of lymphocyte production in lymphatic tissues and organs and of myeloid cells in these same tissues in pathologic and experimental conditions. Myeloid metaplasia of the lymph nodes often begins as an intravascular process by the differentiation of circulating lymphocytes which have hypertrophied and become basophilic hemocytoblasts (identical with large lymphocytes). The germ centers of the follicles, besides producing and destroying lymphocytes, may also produce myelocytes by the proliferation and differentiation of the reticular syncytium and also by the differentiation of lymphocytes. The proof for these conclusions is presented in the form of five colored plates showing accurate drawings. Lang presents the subject from the extreme monophyletic standpoint and gives some of the best evidence available for the direct origin of myeloid cells from lymphocytes and undifferentiated connective tissue cells. He does not attempt to prove that this

occurs under normal conditions, or that the large lymphocyte or hemocytoblast is actually identical with the myeloblast.

The section on "Normal and Pathologic Morphology of the Spleen" (pp. 949-1031) has received adequate treatment by Erich K. Wolff, Berlin. Six pages are devoted to the development of the spleen and its hematopoietic function during the embryonic period. The normal histology, circulation of the blood and normal involution of the "white pulp" are considered at length. The pathology is treated as general pathology and as a series of selected topics among which are: the splenomegalies, the leukemias, the spleen in anemias, especially pernicious, and hereditary hemolytic jaundice.

Hans Hirschfeld, Berlin, gives a well organized critical review of the knowledge of the "Normal and Pathologic Physiology of the Spleen" (pp. 1033-1088). Besides the general physiology of the organ, topics like the following are considered: the spleen in infectious diseases and tumor immunity; its rôle in fat, lipid, protein, carbohydrate and water metabolism; correlated functions of the spleen and other organs, and the splenic hormone. The author cites his own work to prove the influence of the spleen on erythropoiesis in the bone marrow, but concludes that the demonstration of this does not prove the existence of a specific splenic hormone. In the thirteen page bibliography the titles are arranged according to subjects.

The section on "Bone Marrow" by E. K. Wolff (pp. 1089-1130) is brief and leans heavily on the investigations of Maximow for the normal histology. Several of Maximow's excellent figures are reproduced. The origin and development of the different cell lines are considered, and the views of different authors are presented briefly. In the portion of the section dealing with the pathology of the marrow, general features are discussed, but there is considerable detail concerning the changes in the marrow in anemias, in polycythemia, in the leukemias and in tumors of the marrow. It gives a good survey of the principles involved in these changes in the marrow.

In the section on "The Reticulo-Endothelial System" (pp. 1131-1177), Günther Wallbach, Berlin, and E. K. Wolff present a useful critical survey and summary of the knowledge of this system, which can be recommended to all who wish rapid orientation in this difficult field. The subheadings give some idea of its scope: storage of colloidal dyes and iron, bile pigment formation and the reticulo-endothelial system, fat and lipid storage, behavior in infections, immunity, blockade, functional tests, formation of blood cells and proliferative changes, including Gaucher's disease, Niemann-Pick disease, leukemic reticulo-endotheliosis and other conditions. The keen critical discussion of these topics is of special interest.

The section on "Results of Tissue-Culture Experiments with Blood and Blood-Forming Organs" (pp. 1079-1228) by William Bloom, Chicago, is a splendidly illustrated (eight colored plates and twenty-nine text figures) summary of what has been accomplished in this field. Clinical hematology has given abundant evidence for the derivation of lymphocytes, monocytes and myeloblasts from tissue cells (histiocytes), and tissue culture work has shown that the reverse process may also occur; i. e., histiocytes (polyblasts) and eventually fibroblasts may result from transformation of the cells named. Tissue culture has also contributed evidence (Maximow) for the differentiation of genuine lymphocytes to granular leukocytes, thus confirming the results of study of myeloid metaplasia described in the section by F. J. Lang. Those who have not followed the important literature in this field will find this an important chapter for rapid orientation.

The section on "Comparative Morphology of the Blood" by Dietrich Herzog, Giessen (pp. 1229-1318), gives an excellent summarizing, comparative study of the blood of all important groups of animals from sponges to vertebrates, and includes a reproduction of Gulliver's tables of measurements (calculated in microns rather than in fractions of an inch as in the original tables) of erythrocytes and leukocytes, and tables giving total leukocyte and erythrocyte counts and differential counts of various groups of vertebrates. The reader is not smothered with detail, but enough is given to show what may be expected in the different phyla and classes. The section would have been greatly improved by the addition of more figures to the

seven text figures which are presented. The literature, which is scattered through zoological, physiologic and anatomic journals and academy reports, is gathered together in an extensive bibliography.

The relationship between blood cells and the cells which participate in the process of inflammation is discussed by Martin Silberberg, Breslau (pp. 1319-1372). The nine colored plates give proof of the author's views, which coincide in the main with those of Maximow and are based in part on the study of material left by Maximow. The hypertrophy of emigrated hematogenous lymphocytes in the inflamed tissues, or of lymphocytes from cultures of blood to dye-storing histiocytes, and of the latter to fibroblasts, is well illustrated in the plates. The author has no sympathy for the view of von Möllendorff and others that the transformation may be in the reverse direction, i. e., that free histiocytes and lymphocytes may be derived from irritated fibroblasts. Although the discussion is brief, considering the amount of work done in this field, the author manages to refer to most of the modern literature in such a way that one can easily select the titles dealing with any phase of the problem.

I. Zadek, Berlin, has written the chapter on the "Cytology of Exudates and Transudates" (pp. 1373-1418). The five colored plates are probably the best figures that have been published on this subject. This section is especially welcome because hematologic texts give little or no information on this topic. The presentation is from the clinical standpoint and emphasizes the cytologic composition of the exudates of serous and joint cavities in various types of chronic and acute infections and in malignancy. A lengthy discussion is devoted to the exudates of chronic, acute, primary and secondary tuberculosis. Lymphocytosis and the lack of serosa endothelial cells are characteristic of the tuberculous exudate. Endothelial cells are abundant in hydrophilous and mechanical exudates and in malignancy of the bronchi and serous membranes. Genetic relations between serosa cells and lymphocytes are denied. Cells that seem to be intermediate between the two are interpreted as damaged or degenerating lymphocytes. It is the opinion of the reviewer that many of the phagocytic cells described and illustrated as endothelial cells are histiocytes which have originated from lymphocytes which have gradually transformed to the histiocytic type of cell. Such transformations can be seen in almost any experimental exudate from twenty-four to forty-eight hours after the intraperitoneal or intrapleural injection of aleuronat or some other irritant. (See also the section by Bloom.) Experimental exudates and questions of origin and genetic relationships which interest the hematologist receive scant consideration.

The volume is concluded with a clear and concise but comprehensive account of "The Effects of Radium, Kathode Rays, Roentgen Rays and Light Rays on the Blood-Forming Organs and the Blood" (pp. 1419-1520), by Ludwig Halberstaedter and Albert Simons, Berlin, which emphasizes the general effects of radiation and the biologic principles involved, but is not concerned with the details of therapeutic usage. Both the morphologic and the chemical changes resulting from irradiation are considered under the following major headings: changes in the blood-forming organs; effect on the structural elements of the blood; the hematopoietic organs and blood picture after the introduction of radio-active substances; effects on the blood plasma and its chemical constituents and on the coagulation of blood; influence on the sedimentation rate; damage to the blood and hematopoietic organs in professional radiologists.

In conclusion, it may be stated that the great size of the book (1,523 pages) is due to the large number of topics considered rather than to the exhaustive treatment of any one of them. The aim of the editors has evidently been to present a picture and summarizing account of the knowledge without giving an undue amount of detail and without the extensive discussions and speculations that one is accustomed to see in many handbooks. The specialist will wish for more discussion and more proof for many of the conclusions, but he who wishes only rapid orientation will be more than satisfied. The extensive bibliographies, sometimes arranged according to subjects, will facilitate further study.

HAL DOWNEY.

**Practical Hematological Diagnosis.** By O. H. Perry Pepper, M.D., and David Farley, M.D. Cloth. Price, \$6. Pp. 562. Philadelphia: W. B. Saunders Company, 1933.

There has long been a demand for a practical clinical hematologic text in English. This book fills a definite need and contains sufficiently complete discussions of the various aspects of hematology to be of value to the general practitioner. It was not intended to be, and does not serve as, an encyclopedia of hematology.

The book is conveniently divided into three parts. The first part is devoted to the various components of the blood and methods of studying them; the second, to diagnosis of diseases primarily of the blood, and the third, to diseases not primarily of the blood. The laboratory findings in the various diseases are briefly and clearly stated, and the procedures that are most valuable in the differential diagnosis are discussed. The placing of references to key articles at the bottoms of the pages is of advantage. Theoretical discussion has been limited as much as possible, and the terminology has been limited to that used by the authors. A page devoted to a comparison of the terms used for the different cells would not have been amiss, and would have served as a distinct aid to the physician in reading other hematologic literature.

The hematologist will find certain faults. In the discussion of the leukemias there is lack of emphasis regarding the findings in the early stages, or in those cases which run their whole course with total leukocyte counts nearly or entirely within normal limits. Although in most cases of leukemia there is definite and marked leukocytosis when the diagnosis is definitely established, yet many of the patients have consulted their physicians because of symptoms related to the disease, and, because the leukocyte count was found to be nearly normal, the idea of leukemia has been discarded. The impression is obtained that in chronic myelocytic leukemia the leukocyte count is seldom nearly normal except in remission or following treatment for some intercurrent infection. One could hardly agree that the characteristic rise in the percentage of reticulocytes and the later rise in the number of erythrocytes and the percentage of hemoglobin are pathognomonic of addisonian anemia, since these features have been observed in other types of anemia.

The description of the morphologic details of blood does not reach the standard of the rest of the work. The authors' choice of a stain is Wright's modification of the Romanowsky stain. Some of the difficulties with this stain are mentioned, and it is stated that buffer solution, as recommended by McJunkin and Haden, may be used. It would have required only a few lines to give the formula for buffer solution which has solved the staining difficulties in many laboratories. Few of the people for whom this book was intended will have access to the references for this valuable adjunct to staining.

The description of some of the more immature cells is not consistent. Few hematologists would agree that "Its (the myeloblast) size and its nucleus are similar to those of the myelocyte." On page 144 is the statement, "it may be necessary to employ the oxydase stain to distinguish a myeloblastic from a lymphoblastic leukemia," whereas on page 150 is the warning that "the oxydase method cannot be trusted to differentiate the very immature cells of the myelocytic series from the lymphoblasts."

No mention is made of the pink-staining parachromatin as a feature of importance in identifying the normoblast. The differences between normoblast and megaloblast are not clearly defined. The discussion of the morphologic features of infectious mononucleosis is too brief to be of value in diagnosing a disease which constitutes one of the pitfalls of hematologic diagnosis. The changes in the neutrophilic granules in infections are held to be of little practical value, yet it has been shown by careful workers in this field that these changes may precede the nuclear changes in the same cells. The colored plates of the various blood cells are not well reproduced.

In spite of these criticisms, the book is a distinct addition to the library of the general practitioner who is interested in blood, since it serves as a ready reference to almost all phases of hematology and has been shorn of much of the unnecessary detail and discussion of theory and literature so often present in the hematologic textbooks in foreign languages.

**Cancer du côlon droit.** By Jean Gosset. Price, 50 francs. Pp. 328. Paris: Masson & Cie, 1933.

This work of Professor Gosset and his associates represents studies based on fifty patients with cancer of the colon. It is a comprehensive monograph of the subject, with a careful review of the anatomy—including an excellent consideration of the lymphatic drainage—and pathology. The photomicrographs of various specimens are clear and instructive. The author is still undecided as to the value and certainty of endeavoring to classify and establish a prognosis for cancers as suggested by Broders.

Although this is primarily an anatomicosurgical review, there is a rather brief, though excellent, résumé on symptomatology and diagnosis. The author deplores the late recognition of so many cases; in only twenty-six of his fifty cases was resection of the growth possible. The diagnostic value, with excellent illustrations, of the barium enema, combined with the technic of the injection of air, is included. He calls attention to the danger of barium administered orally in cases with obstructing lesions of the colon.

The different surgical procedures are discussed, and Gosset emphasizes the wisdom of a preliminary ileocolostomy and later resection. Ten patients underwent one-stage hemicolectomy, with one death, and sixteen underwent two-stage procedures, with two deaths; this is a splendid report. The gravity of any surgical procedure in inoperable cancer of the bowel is again illustrated, in that in this series there were eleven deaths among the remaining twenty-four patients.

This work may be summarized by stating that it represents an exhaustive review of the literature with discussions of all phases involved in cancer of the right side of the colon.

**Trabajos de la Catedra de Semiologia.** By Prof. T. Padilla. Pp. 664. Buenos Aires: La Semana Medica, E. Spinelli, 1933.

This is a collection of reprints from the department of symptomatology at the National Clinical Hospital in Buenos Aires. Naturally it is impossible to review them all. Most of the papers are on diseases of the heart. Cardiologists will doubtless be interested in the fourth paper, in which Dr. Padilla and his colleagues report their observations in three cases in which a catheter was passed through one of the veins of the arm into the right auricle, and in one case in which the right ventricle was punctured and blood removed. With this technic they were able to determine the minute circulatory volume. In two of the cases the values obtained with the indirect method were practically the same as those obtained with the direct method. In the others there was a difference of 20 per cent between the two figures. In another paper Padilla and Cossio describe the electrical disturbances that appeared when they punctured the right ventricle.

Other studies were made of the outlines of the auricles and ventricles as they project into the shadow of the barium-filled esophagus. Article eleven describes changes in the radiographic image of the heart during auricular fibrillation. In two papers Dr. Cossio describes the bronchial "dancing" up and down due to movements of the heart observed with roentgenocinematography. In this "dance" the bronchi, made visible with iodized poppy seed oil 40 per cent, descend suddenly and rise slowly. The movements are produced by expansion and contraction of the tip of the left auricle.

In article twenty-one there is a discussion of the hemodynamic action of the so-called cardiac hormones which are supposed to form in cases of myocardial insufficiency. Articles twenty-eight and thirty-three are on the treatment of hyperthyroidism with di-iodo-tyrosine.



**Intracranial Tumors.** By Percival Bailey, M.D., Professor of Surgery, University of Chicago. Price, \$6. Pp. 475, with 155 illustrations. Springfield, Ill.: Charles C. Thomas, 1933.

This is an interesting book, well planned and well written. The material is divided into twenty chapters, beginning with an analysis of the problem of tumors in general and ending with the treatment of intracranial tumors, discussing on the way the anatomy of the brain, its physiology and the various manifestations of different tumors which develop in it. These are classified according to the author's views.

The charm of the book lies in the manner in which it is written. The author maintains throughout the volume a very individualistic point of view, describing cases to illustrate the subject under discussion as though he was giving a clinical lecture. Any reader, even if he is only cursorily interested in the subject of tumors of the brain, will gather a great deal of miscellaneous information about a field of medicine and surgery which of late has been intensively cultivated. He will do this pleasantly and easily. The more serious student of cerebral tumors will enjoy the orderly presentation of argument and will appreciate the bibliography of 421 references and the complete index of subject matter which end it.

As Dr. Bailey says in his preface, the method of illustrating the book may cause comment. The book is printed on dull paper and is illustrated with pen-and-ink drawings; roentgenograms are reproduced by diagrams or semischematically. Some readers will agree that this is an improvement in medical illustrating, while others will dislike it. In any event, Dr. Bailey would like to make the intricate subject of the localization and classification of tumors of the brain so interesting that all medical students will wish to understand it. His book is a fine effort toward attaining such a goal.

**Acidosis and Alkalosis.** By Stanley Graham, M.D., Visiting Physician, Royal Hospital for Sick Children, Glasgow, and Noah Morris, M.D., Biochemist, Royal Hospital for Sick Children, Glasgow. Price, \$2.75. Pp. 203. New York, William Wood & Company, 1933.

This is a practical little treatise on acidosis and alkalosis, well written and therefore readable. It appears to have been published for medical students or for clinicians who might wish to brush up on so complex a subject as the reaction of the blood. Accordingly, it is simple in terminology and construction. Such matters as a definition of the terms which are employed, the carbon dioxide dissociation curve and the determination of the state of the acid-base equilibrium are competently handled. Clinical disorders such as diabetes, nephritis, cyclic vomiting and tetany are discussed from the point of view of their pathologic physiology. There is a practical chapter on the ketogenic diet with an appendix giving the ketogenic-antiketogenic values of foods, and methods of preparing molar and normal solutions. On the whole, the book is well worth while. It will prove useful for those for whom it has been written and should have a successful career.

## PRODUCTION OF RETICULOCYTES, ERYTHROCYTES AND HEMOGLOBIN IN ANEMIA

THEIR RESPONSE TO CERTAIN TYPES OF THERAPY

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BOSTON

The magnitude of the rise in reticulocytes following the institution of therapy has been quite generally accepted as a means of evaluating the potency of various substances used in the treatment for pernicious anemia. The rate of the reticulocyte response and subsequent return to a normal level may also indicate the efficiency of the therapeutic substance used.

The magnitude of the response of the reticulocytes will depend to some extent on the method of staining and the technic employed in counting the cells, on the initial erythrocyte count at the time treatment is instituted, on the presence of complicating disease conditions and perhaps on the age of the patient. If these factors are given due consideration, the form and magnitude of the reticulocyte curve serve as a rough index of the potency of various substances used, particularly if treatment is carried out perorally in the usual manner and the amount of potent material used is limited by the patient's ability to ingest the liver substance.

With the introduction of highly concentrated and potent liver extract for parenteral administration, whereby large amounts of active material may readily be given, the magnitude of the reticulocyte response is not directly proportional to the amount of potent material used, nor is the accompanying increase in erythrocytes necessarily directly proportional to the rise in reticulocytes. Consequently, and because the primary object of treatment is to elevate the level of and improve the character of the erythrocytes, it would seem advisable to rely more on increases in the erythrocytes as a means for determining the actual comparative effectiveness of the various substances used.

Riddle and Sturgis<sup>1</sup> gave by stomach tube in a single initial dose large amounts of liver substance as liver extract. Following this treat-

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From the Medical Clinic of the Peter Bent Brigham Hospital.

Read before the Association of American Physicians, Washington, D. C., May 11, 1933.

This study was aided by a grant from the DeLamar Mobile Research Fund of Harvard University.

1. Riddle, M. C., and Sturgis, C. C.: Effect of Single Massive Doses of Liver Extract on Patients with Pernicious Anemia, *Am. J. M. Sc.* **180**:1 (July) 1930.

ment, the reticulocyte response occurred sooner than was customary with smaller initial amounts of material, and, although in some instances there was a maximal peak of response, this was not proportional to the large amount of material used. They concluded that, "the magnitude of the reticulocyte response does not appear to be influenced by the presence within the body of an excessive amount of the active liver principle, a certain maximum number of reticulocytes being possible in any case, the number being related to the original blood level."

Connery and Goldwater<sup>2</sup> observed responses of the reticulocytes of about equal magnitude in patients treated intramuscularly with varying amounts of a concentrated solution of liver extract. The magnitude of the response was perhaps slightly greater for the various doses used than would be expected from maximal amounts of liver substance perorally, although the difference was not great. However, the increase in erythrocytes was more rapid after the larger than after the smaller doses and was more rapid in either case than is generally observed during peroral treatment.

Strauss and Castle<sup>3</sup> have likewise compared the effect of various doses of a solution of liver extract administered intramuscularly. The observations recorded by them indicate that the use of such small doses as that derived from 20 Gm. of liver may initiate a reticulocyte response of the same rate and magnitude as that initiated by a dose derived from 100 Gm. of liver. Neither of the aforementioned amounts of material used, however, produced erythrocytes at the maximum rate possible for the parenteral method of treatment.

Morris, Schiff, Foulger, Rich and Sherman<sup>4</sup> have recently produced interesting reticulocyte responses by the intramuscular administration of concentrated gastric juice. The rate and magnitude of the increase in reticulocytes are essentially similar to those following parenteral liver therapy, but the increase is maintained for many days. In spite of the high and prolonged rise in reticulocytes, the increase in erythrocytes occurred at a minimal rate of speed.

Further evidence that the reticulocyte curve cannot be used as a quantitative measure of the effectiveness of liver substances of all degrees of potency is shown in charts 1 and 2.

Patients treated by three different methods have been selected for comparison in chart 1, so that the initial erythrocyte levels and the

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2. Connery, J. E., and Goldwater, L. J.: Parenteral Use of Liver Extract in the Treatment of Pernicious Anemia, *J. A. M. A.* **98**:1060 (March 26) 1932.

3. Strauss, M. B., and Castle, W. B.: Parenteral Liver Therapy in the Treatment of Pernicious Anemia, *J. A. M. A.* **98**:1620 (May 7) 1932.

4. Morris, R. S.; Schiff, L.; Foulger, J. H.; Rich, M. L., and Sherman, J. E.: Treatment of Pernicious Anemia, *J. A. M. A.* **100**:171 (Jan. 21) 1933.

peaks of the reticulocyte responses are about the same in each case compared. The rate of the reticulocyte response varied, however, according to the type of treatment used, being most rapid following intramuscular injections. In spite of the fact that there is little difference in the magnitude of the reticulocyte responses, the increase in erythrocytes was definitely more rapid in the patient treated intramuscularly.

Ordinarily the reticulocyte response occurs more quickly with intramuscular than with peroral therapy. That this is not entirely respon-

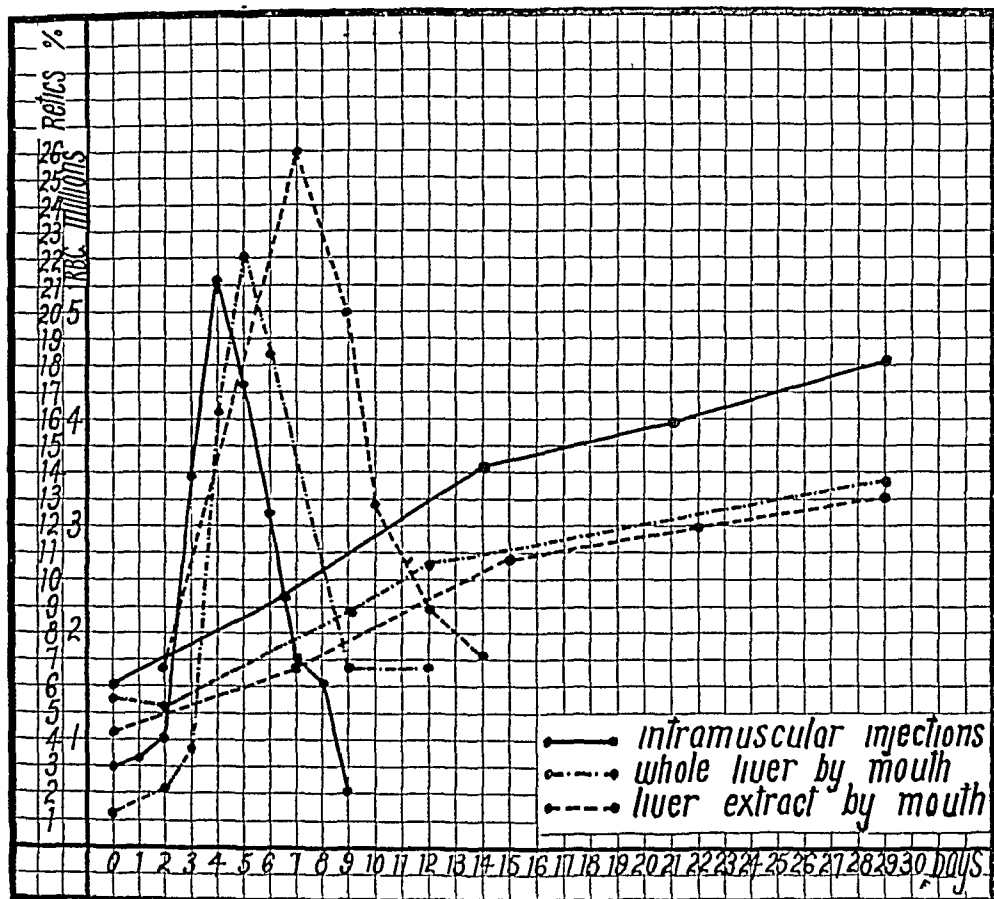


Chart 1.—A comparison of the rate of increases in erythrocytes in three patients who were treated by various means and in whom the initial concentration of erythrocytes and the magnitude of the increases in reticulocytes are comparable.

sible for the more striking increase in erythrocytes with the former method of treatment is illustrated in chart 2. An unusually slow response of the reticulocytes occurred following the intramuscular injection, but the erythrocyte response took place at about a maximum rate.

That the initial dose of concentrated solution given intramuscularly to one patient shown in each chart was actually far more potent than the amounts of liver or liver extract given to the other patients during the first few days of treatment is indicated by a comparison of the

amounts of liver from which the treatment of the various patients was derived. Each of the patients shown in the charts as having been treated intramuscularly received an initial injection of 6 cc. (derived from 200 Gm. of liver) of a concentrated solution of liver extract,<sup>5</sup> followed within twelve hours by a similar injection. After from seven to fourteen days each received 3 cc. (derived from 100 Gm. of liver) and a similar injection every seven days thereafter. The patients who received liver extract perorally received the amount derived from 300 Gm. of liver daily, and the other patient received 300 Gm. of liver prepared as the raw pulp daily.

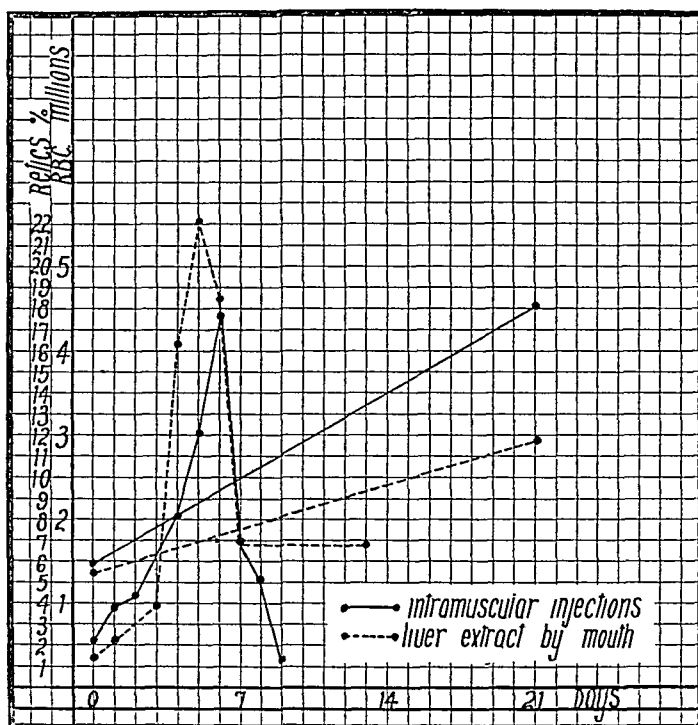


Chart 2.—A comparison of the rate of increases in erythrocytes in two patients as in chart 1 (see text).

Although in general the reticulocyte responses following the use of a concentrated liver extract intramuscularly are somewhat greater than those occurring with peroral treatment, the increases in erythrocytes are usually greater than might be anticipated from the height to which the reticulocytes rise. The increases in erythrocytes are also more constant and uniform than are the rises in reticulocytes. The average and the maximum and minimum peaks of the reticulocyte responses for various initial blood levels in forty-eight patients treated with the concentrated solution of liver extract after the manner previously described are

5. Solution liver extract-parenteral (N.N.R.) Lederle Laboratories, Inc.

shown in chart 3. The interval from the initiation of treatment to the peak of the rise has been rather constant; in four instances three days; in twenty-eight, four days; in nine, five days; in six, six days, and in one, seven days. The interval shows no definite variation dependent on the initial blood levels.

The magnitude of the increases in erythrocytes in this same group has been singularly uniform for those patients with comparable initial

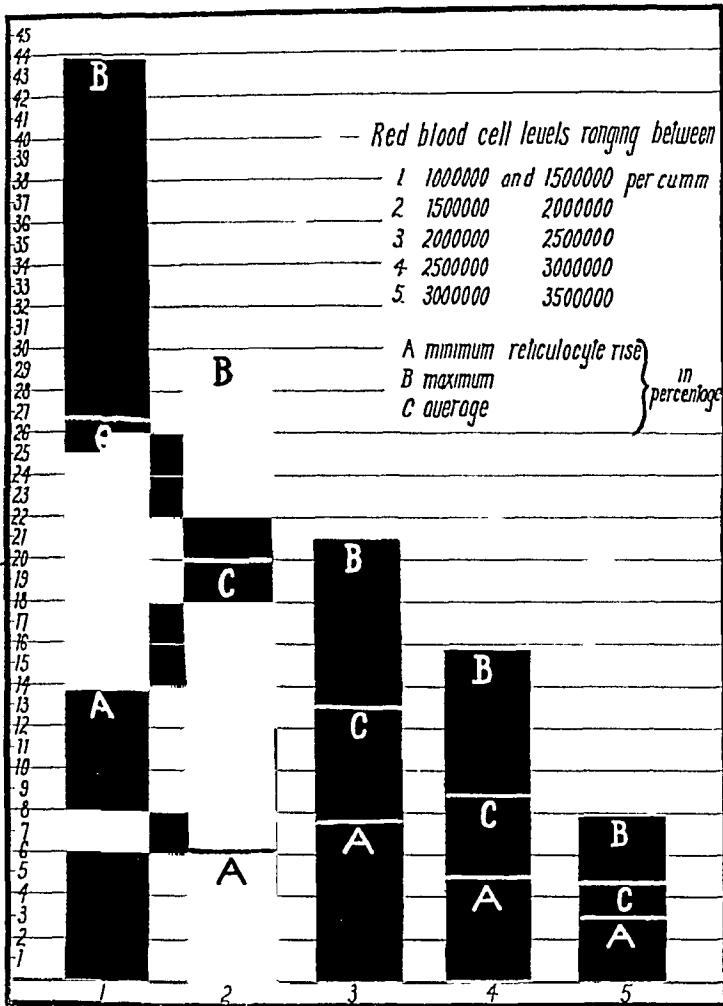


Chart 3.—The reticulocyte responses occurring at various initial red blood cell levels in patients treated with intramuscular injections of liver extract.

blood levels, and the gains have been distinctly more striking than those which have been observed previously with other forms of treatment. The average weekly and daily increases in the erythrocytes over various intervals and grouped according to the level when treatment was started are shown in the accompanying table. In order to compare these increases with those expected during peroral therapy, a curve showing the rate of increase observed in forty-two patients is presented in chart

4, together with a curve published by Minot and Murphy<sup>6</sup> in 1927, showing the improvement in ninety patients observed during treatment with whole liver. It is of interest to note that the former group attained an average erythrocyte level in six weeks equal to the average maximum level reached by the latter group during six months of treatment.

Minot<sup>7</sup> recently stated that if liver in amounts of 300 Gm. or liver extract No. 343 (N. N. R.) derived from 500 Gm. of liver is given daily (perorally), the concentration of red blood cells usually increases by about 2,500,000 cells (an average of 80,000 per day) in thirty days, when the concentration of the cells is less than 2,000,000 per cubic

*Average Increases in the Number of Red Blood Cells Following Intramuscular Injections of Liver Extract*

Initial Erythrocyte Levels		Interval, Days	Average Increase	Average Increase per Day
Ranging Between	Average per C.Mm.			
1,000,000 and 1,500,000	1,230,000	7	840,000	120,000
		14	1,790,000	128,000
		21	2,410,000	114,000
		28	3,050,000	109,000
1,500,000 and 2,000,000	1,750,000	7	720,000	103,000
		14	1,370,000	98,000
		21	1,840,000	88,000
		28	2,370,000	85,000
2,000,000 and 2,500,000	2,260,000	7	620,000	89,000
		14	1,250,000	89,000
		21	1,450,000	69,000
		28	1,760,000	63,000
2,500,000 and 3,000,000	2,740,000	7	510,000	73,000
		14	1,050,000	75,000
		21	1,500,000	71,000
		28	1,820,000	65,000
3,000,000 and 3,500,000	3,340,000	7	380,000	54,000
		14	980,000	70,000
		21	1,120,000	53,000
		28	1,070,000	38,000

millimeter, "or about as fast as it is possible for these elements to be manufactured." The average increase in the concentration of red blood cells during a period of twenty-eight days in a consecutive series of twenty patients with an initial concentration of cells less than 2,000,000 per cubic millimeter treated by means of intramuscular injections,<sup>5</sup> as described previously in this paper, was 2,700,000 per cubic millimeter, or an average of about 100,000 cells per day. This increase is about 25 per cent more rapid than that occurring with optimal peroral treatment as described by Minot. Increases as great as from 3,400,000 to 3,800,000 cells in twenty-eight days, or from 120,000 to 135,000 per day, are frequent. Whether or not this is a maximum rate remains

6. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, *J. A. M. A.* **89**:759 (Sept. 3) 1927.

7. Minot, G. R.: The Importance of the Treatment of Pernicious Anemia on a Quantitative Basis, *J. A. M. A.* **99**:1906 (Dec. 3) 1932.

to be seen. Evidence available now indicates that only a portion of the active substance in the liver extract is utilized immediately in producing these striking responses, and that a fairly large portion is stored to be used as needed. Further concentration of the liver extract or the development of some other substance in the future may initiate even more rapid increases.

Another illustration of the rate of action of the liver material used intramuscularly is given in chart 5. Although the rate of the formation of erythrocytes varies inversely with the initial blood level, as has been previously shown, the rate is such in each group that an erythro-

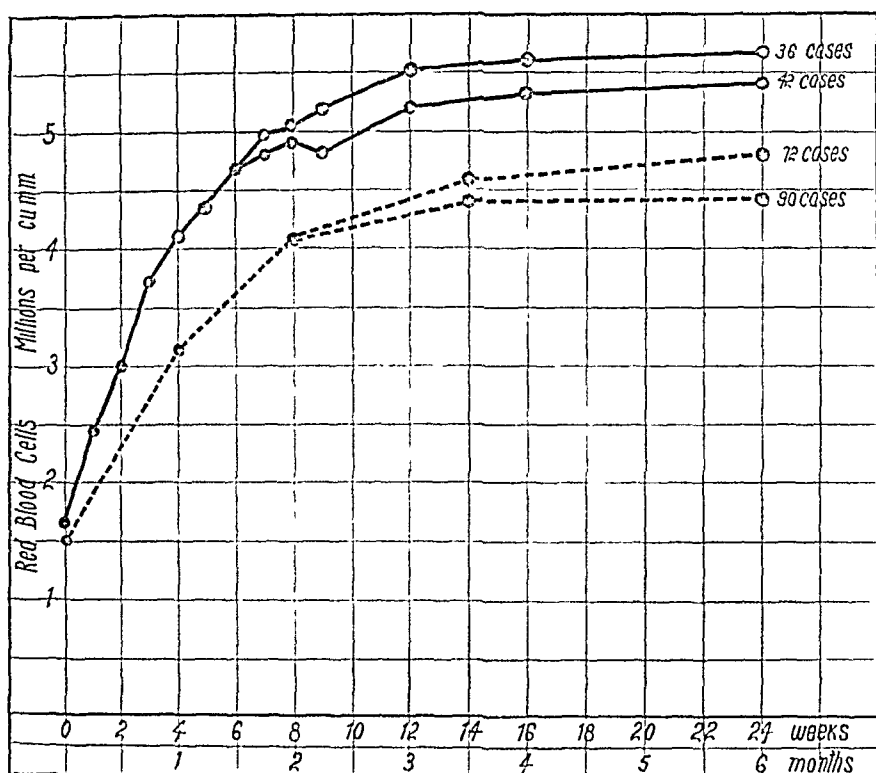


Chart 4.—A comparison of the average rate of improvement of the red cells in patients treated with whole liver and with intramuscular injections of liver extract. The dotted curve indicates the patients treated with whole liver (reproduced from Minot and Murphy<sup>6</sup>). The continuous curve represents the patients treated with intramuscular injections of liver extract. The lower line of each curve includes also those patients with complications or receiving inadequate treatment.

cyte level of between 4,000,000 and 4,500,000 cells per cubic millimeter is reached in twenty-eight days. From then on improvement takes place in each group at approximately the same rate.

The influence of iron therapy in addition to the injections of liver extract is well illustrated in chart 6. Improvement in the hemoglobin during the first few weeks occurs at essentially the same rate whether or not iron is given. At some time during the course of parenteral



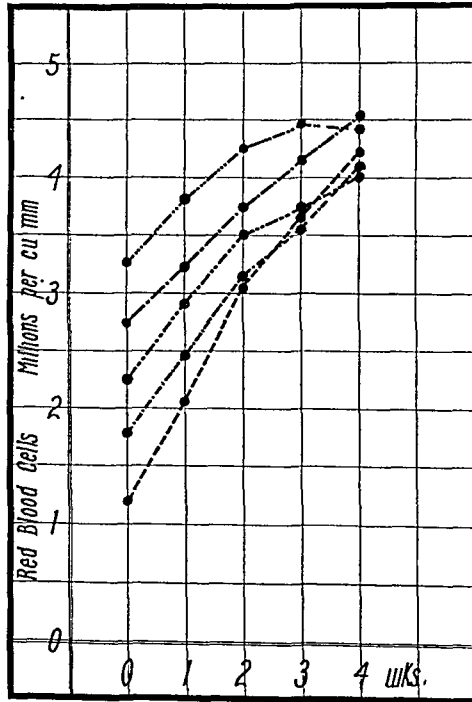


Chart 5.—Progress of the formation of red blood cells during one month of intramuscular treatment. The averages are grouped according to the initial blood levels.

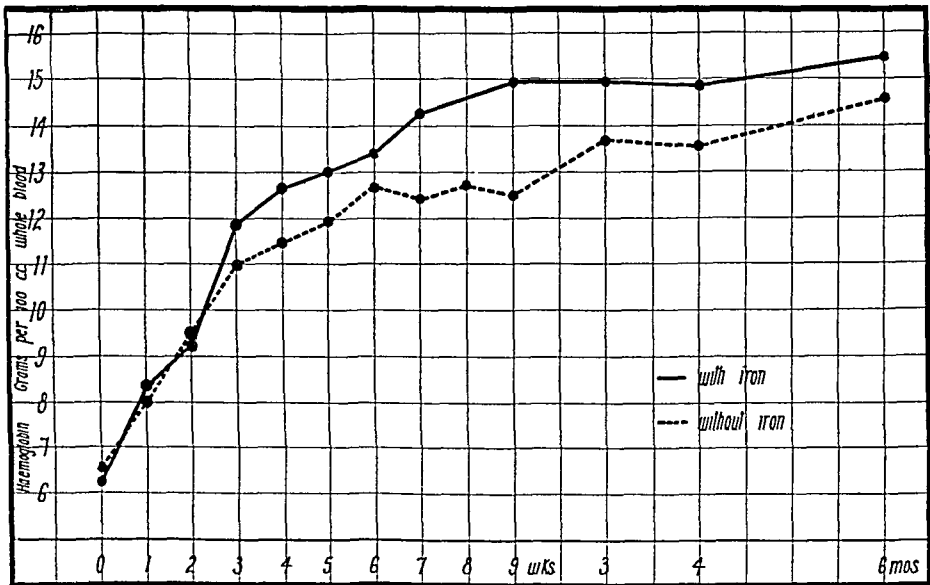


Chart 6.—A comparison of the average rate of improvement of the hemoglobin in patients with pernicious anemia treated with and without iron, together with intramuscular injections of liver extract.

treatment, usually within from three to five weeks after it is started, the use of iron gives an added stimulus to the increase in erythrocytes and hemoglobin. The definite lag in hemoglobin observed in those patients who did not receive iron, as shown in the lower curve of chart 6, will be seen to occur shortly before the time that there is a definite flattening in the upper curves of chart 4. This slowing up of the formation of erythrocytes owing to the developing deficiency in iron is, no doubt, more abrupt than might otherwise be expected.

#### COMMENT

It is well known that the magnitude, and to some extent the rate, of the response of the reticulocytes to therapy is in part dependent on the method of staining and technic of counting the reticulocytes, the number of erythrocytes present when treatment is started and the state of health of the patients in certain respects other than the anemia.

If the various secondary factors which influence the rise in reticulocytes are assumed to be constant, the magnitude of the response of the reticulocytes will indicate the potency of the material used if it is administered in submaximal amounts. The data presented, particularly for patients treated with maximal amounts of potent material, as with a concentrated solution of liver extract administered intramuscularly, indicate that a reticulocyte response of equal magnitude may be observed following the use of varying amounts of equally potent material, that the response will occur more quickly following the initial administration of large amounts, that the magnitude of the increase in erythrocytes may not vary directly with the magnitude and duration of the rise in reticulocytes and that the rate of increase of the erythrocytes is a more accurate indication of the effectiveness and potency of substances used in the treatment of patients with pernicious anemia than is the rate and magnitude of the reticulocyte response.

The explanation for the lack of correlation between increases in reticulocytes and erythrocytes as observed following treatment with various substances is not obvious and is probably not entirely controlled by the condition of the blood-forming organs at the time treatment is started. The variation in response to treatment by different means may be dependent on the rate of absorption or the utilization of the active principle under the various methods of its administration. If this is the case, it is probable that when administered in large amounts, as by intramuscular injection, the active material presented ready for the immediate use of the blood-forming organs causes more rapid maturation of the erythrocytes, so that the proportion of mature to immature cells (reticulocytes) in the circulation is greater than when less of the potent substance is available.

Is it possible, however, that two factors are present in the various materials used in the treatment for pernicious anemia, a stimulating (or reticulocyte-producing) and a maturing (or erythrocyte-producing) one? These may occur in varying proportions in different materials which have been used, the maturing occurring in greater proportion in the more refined and concentrated liver extract for intramuscular use.

In the treatment of the patient whose blood is in a state of relapse, it is desirable that improvement of this condition be promoted as rapidly as possible. Observations indicating an unusually rapid increase in erythrocytes following the intramuscular injection of initial large amounts of a concentrated solution of liver extract <sup>5</sup> (12 cc. prepared from 400 Gm. of liver) and followed by infrequent smaller injections are presented. That this material is of a high degree of potency and that treatment by this means insures optimal efficacy are well illustrated by the improvement shown.

The administration of large doses of iron during treatment with liver extract parenterally is strongly recommended. By this means one may be more certain to obtain the maximum effect of the liver material by preventing the development of deficiency in iron as a result of the rapid maturation of erythrocytes produced by the parenteral method of therapy.

# MACROCYTIC ANEMIA IN DISEASE OF THE LIVER

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SYRACUSE, N. Y.

The cause of the so-called pernicious blood picture is still one of the most interesting fields of study in modern medicine. It is now generally recognized that this type of anemia is merely one variety of faulty formation of blood and not a pathognomonic sign. Whatever disease process is able to bring about this particular disturbance in hematopoiesis may produce this blood picture.

The following introductory case first suggested to me that cirrhosis of the liver might be another such disease process. This case was presented at a medical clinic in the John Hopkins Hospital on March 8, 1931.<sup>1</sup>

A man, aged 50, showed a clinical picture of advanced hepatic cirrhosis together with signs strongly suggestive of pernicious anemia. The liver was markedly enlarged and nodular. The skin was moderately jaundiced (icteric index, 45). There were in addition glossitis, combined sclerosis and a macrocytic type of anemia. The hemoglobin was 70 per cent; the erythrocyte count, 3,000,000, and the color index, 1.15. These findings suggested complicating pernicious anemia. Against pernicious anemia, however, was the normal response of the gastric secretions to histamine. The free hydrochloric acid content was 48 cc. of tenth-normal sodium hydroxide; the total, 64. Necropsy, performed several months later, established the diagnosis as hepatic cirrhosis with "extensive scarring." The cord showed slight diffuse degenerative changes in the posterior columns. The bone marrow was hyperplastic.

This case is one of cirrhosis of the liver in which the blood developed a "pernicious" character; that is, the anemia was of the hyperchromic or macrocytic type as indicated by the high color index. Just why glossitis and combined sclerosis should have been present also cannot be discussed here.

The following questions are of first importance.

1. Is the macrocytic anemia secondary to, or independent of, the hepatic cirrhosis?
2. If it is secondary to the hepatic cirrhosis, can other diseases of the liver also cause this change in the blood?

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From the Medical Service, Syracuse University Hospital.

Read at the Annual Meeting of the Alumni of Syracuse University Medical School, June, 1932.

1. This case is reported with the permission of Dr. Longcope.

3. If they can, might not the presence of a macrocytic anemia be taken, at times, as an indication of disease of the liver?

A few references from the literature will show that the occurrence of a macrocytic blood picture in cirrhosis of the liver has been widely recognized.

In 1913 Babonniex and Tixier<sup>2</sup> reported a case illustrating the "coexistence of cirrhosis and pernicious anemia." They cited two similar cases from the French literature and referred to several discussions on the subject. From these they stated that "it is difficult to draw any definite conclusions," but "all have the merit of attracting attention to the relationship of the cirrhotic to the anemia of the pernicious type."

Naegeli,<sup>3</sup> in his book on diseases of the blood published in 1912, merely included cirrhosis of the liver under the differential diagnosis of pernicious anemia. In a later edition, however, he was more specific,<sup>4</sup> stating that "certain hepatic cirrroses show a high value of hemoglobin and a macrocytosis." Another comment is also significant: "The combination of pernicious anemia with cirrhosis of the liver is not at present clear to me. In one observation the cirrhosis was wholly in the foreground of all the symptoms and the pernicious anemia established later."

In Italy, Gamna made similar observations. In 1926 he<sup>5</sup> reported two cases of pigmentary cirrhosis of the liver in which there was a "tendency of the color index to increase to and above unity." He was impressed with the morphologic quality of the red cells, which showed "an anisomacrocytosis so marked as to call to mind the blood picture of pernicious anemia." In another paper<sup>6</sup> the degree of macrocytosis was reported: "In advanced atrophic cirrhosis there is found a more or less manifest tendency toward an increase in the size of the red cells, such that many of them, ranging from 20 to 25 per cent up to 40 to 45 per cent, surpass a diameter of 9 microns."

Again, in 1932, this interesting relationship was observed by Remen.<sup>7</sup> He reported an illustrative case and gave references to seven

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2. Babonniex, L., and Tixier, L.: Sur un cas de cirrhose compliquée d'anémie pernicieuse, *Gaz. méd. de Nantes* **31**:61, 1913.

3. Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, ed. 2, Leipzig, Veit & Co., 1912, pp. 434 and 429.

4. Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, ed. 4, Berlin, Julius Springer, 1923, pp. 321, 304, 320 and 350.

5. Gamna, C.: Contributo alla patologia ed alla clinica della cirrosi pigmentaria, *Minerva med.* **6**:797, 1926.

6. Gamna, C.: L'anisocitosi dei globuli rossi del sangue, *Minerva med.* **6**:730, 1926.

7. Remen, L.: Perniziöse Anämie und Leberzirrhose, *Med. Klin.* **28**:514 (April 8) 1932.

similar cases found largely in the German literature. The cirrhosis in Remen's case was considered secondary to the pernicious anemia. He added, however, that "cirrhosis of the liver, which at times is followed by a secondary anemia, may in exceptional instances be the cause of a pernicious anemia."

Perhaps the recent cases of Barker<sup>8</sup> and Cabot<sup>9</sup> are also examples of this syndrome. Both show apparently a macrocytic anemia in the presence of hepatic cirrhosis.

I have observed three cases in which disease of the liver was associated with anemia of the macrocytic type. The diameters of the red cells were measured in each case to confirm the macrocytosis and to determine its degree.

#### METHODS

In each case I determined the significant data on the blood, as indicated in the tables. For comparison, the earlier determinations in cases 1 and 3 are recorded from the case histories.

The hemoglobin was measured by the Sahli (Leitz) hemometer, which has a standard of 13.9 Gm. of hemoglobin equivalent to 100 per cent. The red blood cells were counted with a Levy-Hausser counting chamber and pipets. Capillary blood was used throughout.

The diameters of the red blood cells were measured with a Leitz filar micrometer ocular. The counting chamber was used in calibrating the length of the tube. The blood smears were stained with the Groat-Jenner stain. In measuring the diameters of the red cells, only the round cells were chosen, according to the method of Grosh and Stifel.<sup>10</sup> Measurements were made to 0.1 micron and the groupings arranged to correspond with those of Price-Jones.<sup>11</sup> The control curve was made from the blood of two normal healthy persons. In each instance 500 cells were measured.

The question of the serum bilirubin raising the hemoglobin value in patients showing jaundice was also considered. In two cases in which the icteric index was 100, the serum alone raised the hemoglobin less than 3 per cent. As none of the three cases to be reported showed an icteric index of over 100 at any time, this occasional small factor of error has been disregarded.

#### REPORT OF CASES

##### CASE 1.—*Diffuse Chronic and Acute Hepatitis (Pathologic Diagnosis).*

*History.*—A. I., a man, aged 30, was admitted to the hospital on April 21, 1931, complaining of swelling of the abdomen of four months' duration.

8. Barker, L. F.: Cirrhosis of the Liver with Ascites, Splenomegaly, Secondary Anemia and Endocrinopathies in a Girl of Seventeen, *M. Clin. North America* **14**:99 (July) 1930.

9. Cabot, R. C.: A Cirrhosis Problem: Biliary Versus Laennec's, Case 17282, *New England J. Med.* **205**:107 (July 9) 1931.

10. Grosh, L. C., and Stifel, J. L.: The Diameter of the Red Blood Cells in the Differentiation of Anemias, *Arch. Int. Med.* **36**:874 (Dec.) 1925.

11. Price-Jones, C.: Diurnal Variation in the Sizes of Red Blood Cells, *J. Path. & Bact.* **23**:371 (Dec.) 1920.

For five years the patient had been working in a battery repair shop. His special duties, those of recharging batteries, required his almost continual presence in a closed room frequently cloudy with fumes. Although he had noticed an increase in infections of the upper respiratory tract, general weakness and occasional gastric upsets, he persisted at work until shortly before admission. For about four months the size of the abdomen had been gradually increasing. He had never been a heavy drinker.

*Physical Examination.*—When admitted the patient was not acutely ill, but suffered from abdominal distention. The skin was slightly jaundiced. Following the aspiration of a liter of ascitic fluid, the liver could be palpated a full hand-breadth below the costal margin. Its surface was fairly smooth and somewhat tender; the edge was firm. The spleen was not palpated.

*Course.*—In spite of frequent aspirations followed by temporary relief, the course continued downhill. Anemia gradually developed, at first of the microcytic type, and later macrocytic. A moderate degree of jaundice appeared and persisted until

TABLE 1.—*Determinations of Blood in Case 1*

Date	Hemoglobin, per Cent	Red Cells per C.Mm.	Color Index	Number of Estimations	Icteric Index
April 25 to April 26.....	91	5,090,000	0.89	2	15
June 30 to July 23.....	82	4,730,000	0.86	5	50
August 3, operation					
August 6 to August 17.....	75	4,010,000	0.90	3	..
September 2 to September 12.....	75	3,420,000	1.10	2*	..
October 25, discharge					
December 28 .....	90	4,440,000	1.01	1*	..

\* My determinations.

shortly before discharge. Three months after admission an exploratory laparotomy was performed in order to establish the diagnosis. A small piece of liver was removed, and the gallbladder drained. On October 10, after a stormy convalescence of two months, the patient was discharged as improved. Ascites had not recurred after closure of the wound.

*Clinical Diagnosis.*—This diagnosis was hypertrophic biliary cirrhosis.

*Laboratory Data.*—Biopsy showed diffuse chronic and acute, periportal and pericentral hepatitis.

The ascitic fluid was a cloudy yellow; the specific gravity was 1.020. Inoculation into a guinea-pig gave negative results. During fasting the stomach contents showed free hydrochloric acid, amounting to 16 cc. of tenth-normal sodium hydroxide; total, 29. After an Ewald test meal there was no free hydrochloric acid, and the total amounted to but 19, owing probably to a regurgitation of duodenal contents. The patient refused further passage of the stomach tube. The Wassermann reaction of the blood was negative. The stained red cells showed slight anisocytosis and poikilocytosis, but no megaloblasts or normoblasts were found. On September 12 the mean diameter of the red cells was 7.92 microns.

CASE 2.—*Chronic Hepatitis or Hepatic Cirrhosis (Clinical Diagnoses).*

*History.*—T. M., a man, aged 52, of Irish descent, was admitted to the hospital on Dec. 9, 1931, complaining of nausea associated with painless jaundice. The jaundice had been noticed about a month, and the nausea, a few weeks before that.

The patient was a barber, but for the past thirty years he had been the proprietor of a small hotel. He admitted an almost continuous indulgence in alcoholic drinks. Nevertheless, his health had been good until about a month before admission, when he noticed increasing weakness, loss of weight, yellowness of the skin and frequent attacks of nausea without vomiting.

*Physical Examination.*—Besides deep jaundice, enlargement of the liver was the only significant finding. The firm edge of the liver could be palpated four finger-breadths below the costal margin. The surface was fairly smooth, but not tender. There was no demonstrable ascites or splenomegaly.

*Course.*—The patient remained in the hospital nearly six weeks, his temperature continuing normal throughout. One unsuccessful attempt at duodenal drainage was made. The jaundice cleared up gradually, but was still noticeable when the patient was discharged, on Jan. 19, 1932. Four months later the patient was again examined. The liver was found still greatly enlarged, though the jaundice had disappeared. Seven months after this a second check-up examination was made. The liver was considerably reduced in size, being palpable only within the costal angle.

TABLE 2.—*Determinations of the Blood in Case 2*

Date	Hemoglobin, per Cent	Red Cells per C.Mm.	Color Index	Number of Estimations	Icteric Index
Dec. 9, 1931, to Jan. 8, 1932.....	90	3,960,000	1.13	14*	80-100
January 19, discharge.....	..	.....	....	..	20
May 5 .....	92	4,250,000	1.07	2*	5
December 1 .....	94	4,940,000	0.95	2*	2

\* My determinations.

*Diagnosis.*—At first the possibility of acute infectious jaundice was considered, but the subsequent course did not bear this out. The final diagnosis rested between duodenitis with ascending infection of the biliary tract and beginning alcoholic cirrhosis.

*Laboratory Data.*—Following an Ewald test meal the gastric contents showed free hydrochloric acid, amounting to 34 cc. of tenth-normal sodium hydroxide; total, 52. The Wassermann reaction of the blood was negative. The stained red cells showed the same minor variations as in case 1. On December 10, the mean diameter of the red cells was 8.09 microns.

### CASE 3.—*Hepatic Cirrhosis with Diffuse Hepatitis (Pathologic Diagnosis).*

*History.*—N. F., an English widow, aged 49, was admitted to the hospital on Nov. 9, 1931, complaining of intermittent diarrhea and general weakness of about one month's duration.

Following an attack of erysipelas three years before, a spastic gait developed, and the patient had much difficulty in walking. Since then there had been a gradually increasing generalized weakness, associated on admission with intermittent diarrhea.

*Physical Examination.*—The patient was very much underweight and extremely weak. At first she was unable to stand alone. The skin appeared somewhat pigmented over both extremities bilaterally. Marked chorioretinitis of uncertain origin was found. At the base of the left lung a few moist râles were heard.



When the patient was able to walk, she showed spastic paraplegia of the lower extremities. At that time examination of the abdomen revealed nothing unusual.

*Course.*—After an afebrile illness of five weeks' duration, the patient was discharged on December 19. Her condition was improved, but no diagnosis had been made. On April 4, 1932, between three and four months later, she was readmitted to the hospital, complaining of abdominal swelling of two weeks' duration. This time ascites was present, and there was in addition a moderate degree of jaundice (icteric index, 36). An exploratory laparotomy was performed. The patient died a few days later.

*Necropsy Observations.*—Besides the ascites and jaundice, the presence of a small, distorted liver was the only significant gross finding. Microscopic examination of the liver showed marked cirrhosis, probably of Laënnec's type, together with marked chronic and acute periportal hepatitis and areas of acute focal necrosis.

*Laboratory Data.*—On gastric analysis, the first specimen after the injection of histamine showed a free hydrochloric acid content of 37 cc. of tenth-normal sodium hydroxide, and a total of 49. The Wassermann reaction of the blood was negative. The stained red cells were no more unusual than in the other two cases. On April 27, the mean diameter of the red cells was 7.81 microns.

TABLE 3.—*Determinations of the Blood (Case 3)*

Date	Hemoglobin, per Cent	Red Cells, per C.Mm.	Color Index	Number of Estimations	Icteric Index
November 9 to December 14.....	78	4,350,000	0.87	5	..
April 27, 1932.....	81	3,860,000	1.05	2*	36

\* My determination.

Although the color index of 1.05 in case 3 cannot be considered definitely above normal, the decrease in the red cells of nearly 500,000 per cubic millimeter, the hemoglobin remaining at essentially the same level, indicates clearly a macrocytic change in the blood.

#### SUMMARY OF CASES

The significant features in these three cases may be summed up as follows: In the first two, a definitely high color index was present during some period of the anemia; in the third, a macrocytic change in the red cells had taken place between admissions. In all three cases the stained red cells showed only slight anisocytosis and poikilocytosis. Free hydrochloric acid was demonstrated in the gastric contents of each patient. Disease of the liver was confirmed pathologically in cases 1 and 3, and was diagnosed clinically in case 2. Except in case 3, in which the possibilities of sprue and pellagra were eliminated at necropsy, there was no evidence to indicate the presence of any significant complication.

#### CURVES OF THE DIAMETER OF THE RED CELLS

The macrocytic character of the anemias is more clearly demonstrated by the accompanying chart. The curves represent graphically the diameters of the red cells, measured according to the method of Price-

Jones.<sup>11</sup> Curves of normal blood and of that in pernicious anemia are included for comparison.

The curve averaging the three cases of disease of the liver is seen to the right of the normal curves, and approaching that of pernicious anemia. It does not show the so-called spread characteristic of the curve of pernicious anemia, but demonstrates clearly the increased size of the red cells. The mean diameters correspond to the relative positions of the curves.

It may be added that individually, as well as taken together, the cases of disease of the liver show a mean diameter of the cells above

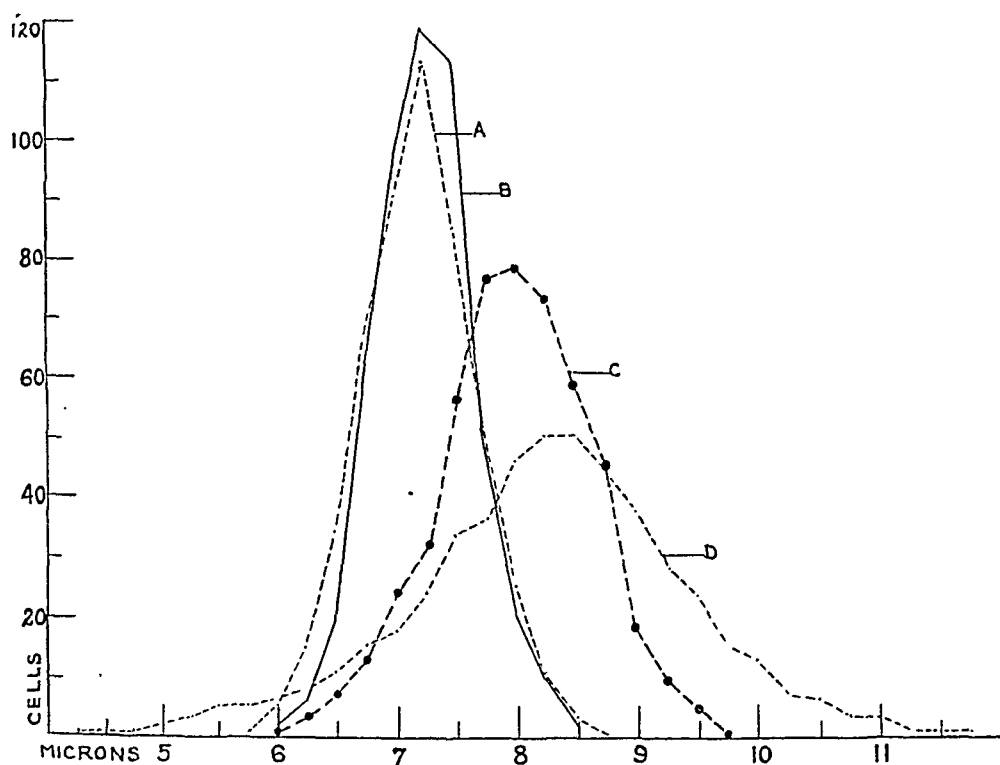


Chart showing the average curves of the diameters of the red cells in health, in disease of the liver and in pernicious anemia. *A*, Price-Jones' normal, averaging 100 curves (Price-Jones, C.: *J. Path. & Bact.* **32**:479 [July] 1929). *B*, my normal, averaging 2 curves. *C*, my cases of disease of the liver, averaging 3 curves. *D*, Price-Jones' cases of pernicious anemia, averaging 20 curves (Price-Jones, C.: *J. Path. & Bact.* **25**:487 [Oct.] 1922). The mean diameters are as follows: *A*, 7.20 microns; *B*, 7.26 microns; *C*, 7.94 microns, and *D*, 8.24 microns.

the estimated upper limit of normal determined as 7.72 microns by Price-Jones.<sup>12</sup>

These findings are additional evidence that the anemia associated with these cases of disease of the liver was of the macrocytic type.

12. Price-Jones, C.: Red Blood Cells in One Hundred Healthy Persons and in Pernicious Anemia, *J. Path. & Bact.* **32**:479 (July) 1929.

## INCIDENCE OF MACROCYTIC ANEMIA IN HEPATIC CIRRHOSIS

To determine the incidence of macrocytic anemia in hepatic cirrhosis, the records of the hospital were consulted. Twenty-eight cases so diagnosed contained sufficient data for use. Of these twenty-eight, five, or 18 per cent, showed a high color index in the presence of anemia. For the five cases, the hemoglobin ranged between 33 and 87 per cent, averaging 65 per cent. The red cells numbered from 1,100,000 to 3,750,000 per cubic millimeter, averaging 2,470,000. The color index varied from 1.16 to 1.56, with an average of 1.35.

As control series, the cases of the patients with acute infectious jaundice and proved cholelithiasis admitted over the same period were reviewed. There were fourteen of the former and forty-five of the latter. None showed macrocytic anemia.

TABLE 4.—*Incidence of Macrocytic Anemia in Hepatic Cirrhosis, Acute Infectious Jaundice and Cholelithiasis*

	Number of Cases	Number Showing Macrocytic Anemia	Percentage
Hepatic cirrhosis .....	28	5	18
Acute infectious jaundice.....	14	0	0
Cholelithiasis .....	45	0	0

The figure of 18 per cent given in table 4 is probably somewhat high. Many of the cases of hepatic cirrhosis lacked laboratory data and could not be tabulated.

These findings suggest, however, that macrocytic anemia occurs not infrequently in hepatic cirrhosis, while it perhaps never occurs as secondary to acute infectious jaundice or uncomplicated cholelithiasis.

## COMMENT

The anemias have been classified by Wintrobe<sup>13</sup> according to recent conceptions, depending on the difference in size and hemoglobin content of the red cell. He considers a macrocytic, a normocytic and two microcytic types. In the macrocytic type the cells are distinctly larger than normal, and the color index is uniformly high. This type is "notably represented by pernicious anemia in relapse," but may also be found occasionally in other conditions.

Just why macrocytic anemias develop at all is not yet clearly understood. The mechanism involved, however, has been partially brought

13. Musser, J. H., and Wintrobe, M. M.: Diseases of the Blood, in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1920, vol. 6, pp. 753 and 843.

to light by Castle and his associates<sup>14</sup> in their studies of pernicious anemia. In considering this mechanism, the function of the liver will be seen to occupy an important position.

In 1929 Castle and Townsend<sup>14a</sup> showed that pernicious anemia is dependent on a deficiency in gastric secretion. This deficiency is almost invariably associated with, though not necessarily due to, achylia gastrica. According to Castle, the mucosa of the stomach normally secretes a substance, the "intrinsic factor," which acts on certain ingested proteins ("extrinsic factor") to form a principle which is active in regeneration of the blood ("effective principle"). If the secretion of the intrinsic factor is deficient, the active principle will not be formed, and pernicious anemia will result, at least hematologically. The feeding of liver supplies this principle preformed, and thereby causes the remission.

So much appears to be accepted. What becomes of the active principle under normal conditions and how it acts either normally or in pernicious anemia are still questions. Undoubtedly, it first passes through the portal vein to the liver, where it is taken up and to a large extent stored, the end-result of its presence in the body being normal hematopoiesis. The hematopoietic function is probably performed indirectly, either in building up Whipple's "parent pigment substances,"<sup>15</sup> in the possible production of some specific liver hormone,<sup>16</sup> or in regulating some phase of fat metabolism, such as the formation of cholesterol.<sup>17</sup>

Whatever the intricate steps may be, the function of the liver is undoubtedly concerned. In 1928 Schwarz<sup>18</sup> accepted some such function and explained the effect of the feeding of liver in pernicious anemia as equivalent to its restoration. He concluded that "only when this

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14. (a) Castle, W. B., and Townsend, W. C.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *Am. J. M. Sc.* **178**:764 (Dec.) 1929; (b) Castle, W. B.; Townsend, W. C., and Heath, C. W.: III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle, Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, *ibid.* **180**:305 (Sept.) 1930.

15. Whipple, G. H.: Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch. Int. Med.* **29**:711 (June) 1922.

16. Harris, S.: The Etiology of Pernicious Anemia: Is It Secondary to Hepatic Infection, Resulting in Deficiency of a Liver Endocrin? *Tr. Am. Gastro-Enterol. A.* **31**:208, 1928.

17. Muller, G. L.: The Relation of Cholesterol, Lecithin Phosphorus and Fatty Acids to the Remission of Pernicious Anemia, *Am. J. M. Sc.* **179**:316 (March) 1930.

18. Schwarz, E.: Megaloblastische Blutbildung und Leber, *Wien. klin. Wchnschr.* **41**:192 (Feb. 9) 1928.

definite but at present unknown function of the liver cells fails, do macrocytic and megaloblastic anemias develop."

It is now important to show that several conditions have been associated with macrocytic anemia, in which disease of the liver is an outstanding feature. Before considering these special conditions, however, the better known causes of the "pernicious blood picture" should first be reviewed. The latter seem to fall into two main groups.

The first group includes those which, according to Castle and his associates,<sup>14b</sup> are characterized by persistent symptoms of the gastro-intestinal tract. There is here a probable disturbance in either the formation or the absorption of the final effective principle. It consists in pernicious anemia, sprue, pellagra and some rarer intestinal disorders.

In the second group are the so-called chronic hemolytic anemias in which blood hemolysis is an assumed factor. Under this heading, Musser and Wintrobe<sup>18</sup> have placed hemolytic anemia of pregnancy, tapeworm anemia, hemolytic anemia of gastro-intestinal carcinoma and, possibly, certain anemias associated with tertiary congenital syphilis.

Rarely, the macrocytic blood picture may also occur in leukemia and malignant metastases to the bone marrow.<sup>19</sup>

Now may be considered the conditions in which disease of the liver is apparently an outstanding feature. These could be classified into a third distinct group. They include erythroblastosis foetalis, congenital syphilis, anemia infantum pseudoleukaemica, arseniuretted hydrogen gas poisoning, complicated disease of the gallbladder and cirrhosis of the liver. Each will be taken up separately to emphasize the association of macrocytic anemia with pathologic changes in the liver.

*Erythroblastosis Foetalis.*—This is a disease of early infancy, showing marked disturbances in the formation of blood. Naegeli<sup>8</sup> considered the blood picture as frequently simulating that of pernicious anemia. Recently, Diamond and his co-workers<sup>20</sup> have discussed the blood findings in twenty cases. They observed almost uniformly a marked macrocytic anemia. In each case the liver was greatly enlarged and showed "large numbers of islands of hematopoiesis scattered throughout the parenchyma."

*Congenital Syphilis.*—Although less frequently observed than in erythroblastosis foetalis, macrocytic anemia may be a prominent feature of congenital syphilis. The blood pictures may be indistinguishable.<sup>20</sup>

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19. Cornell, B. S.: The Etiology of Pernicious Anemia, *Medicine* 6:375 (Sept.) 1927.

20. Diamond, L. K.; Blackfan, D. K., and Baty, J. F.: Erythroblastosis Fetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum and Anemia of the Newborn, *J. Pediat.* 1:269 (Sept.) 1932.

Regarding the liver in congenital syphilis, according to MacCallum,<sup>21</sup> "perhaps the commonest change is a general retardation in its development, so that at birth it still appears as an organ actively engaged in blood formation."

*Anemia Infantum Pseudoleukaemica.*—This is a third disease of early infancy in which the anemia may also be macrocytic. Shilling<sup>22</sup> stated that the blood picture may be "at times rather pernicious, at other times distinctly leukemoid." Naegeli,<sup>4</sup> in considering anemias with a high color index and macrocytosis, included "severe forms of anemia in infancy, especially anemia infantum pseudoleukaemica." In the liver, in this condition, he found that "intra-acinous erythropoiesis is outspoken."

These three anemias of infancy might be considered together, since the parenchyma of the liver shows blood-forming islands in each. As this pathologic change suggests, the liver may have failed to assume its adult erythropoietic function, and, therefore, to have reverted to its embryologic one.

On the other hand, the following three conditions may be considered as showing impairment of this function subsequent to a normal state of activity.

*Arseniuretted Hydrogen Gas Poisoning.*—Dudley,<sup>23</sup> in 1919, reported thirty cases of poisoning due to the arsenic-contaminated gas evolved from batteries on a submarine. Of the thirty patients, twelve showed definite macrocytic anemia. All recovered without specific treatment. The symptoms were varied except in one respect—jaundice was uniformly present. Excessive destruction of blood cannot account for the jaundice in those cases in which there was no anemia. It was more probably of hepatic origin and due to toxic hepatitis.

*Complicated Disease of the Gallbladder.*—In 1924, Jones and Joyce<sup>24</sup> reported thirteen cases of disease of the gallbladder showing a blood picture resembling pernicious anemia. In five cases the anemia disappeared after cholecystectomy. These authors brought forth evidence "pointing to the presence of hemolyzing or other micro-organisms in the wall of the gall-bladder as being the possible cause of idiopathic progressive pernicious anemia." A study of the cases in this and a

21. MacCallum, W. G.: A Textbook of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932, p. 757.

22. Shilling, V.: The Blood Picture, St. Louis, C. V. Mosby Company, 1929.

23. Dudley, S. F.: Toxemic Anemia from Arseniuretted Hydrogen Gas in Submarines, J. Indust. Hyg. 1:215 (Sept.) 1919.

24. Jones, N. W., and Joyce, T. M.: Infections of the Gall Bladder in Relation to Pernicious Anemia, Am. J. M. Sc. 168:469 (Oct.) 1924.

subsequent report <sup>25</sup> suggests that in the cases in which the findings and course were not characteristic of true pernicious anemia, the macrocytic picture was due to disease of the liver. One patient in whom free hydrochloric acid was present in the gastric contents and whose blood returned to normal following cholecystectomy died six years later of "progressive obstructive biliary cirrhosis." In this case, as in others, an infection of the biliary tract resulting in hepatitis may well be assumed.

*Hepatic Cirrhosis.*—It has already been shown that macrocytic anemia occurs in cirrhosis of the liver. Disease of the liver is here, of course, understood.

There does exist, then, a distinct group of conditions which are associated with a macrocytic type of anemia and in which disease of the liver is apparently an outstanding feature. Assuming that the function of the liver plays a part in normal erythropoiesis, the pathologic changes in that organ might be held indirectly responsible for the development of the macrocytic blood picture. This answers in the affirmative the first two questions suggested by the introductory case.

The third question seems also to require an affirmative answer; that is, macrocytic anemia may, at times, be taken as an indication of disease of the liver. Subject to future confirmation, this offers a diagnostic sign which may be illustrated as follows: If a patient shows a macrocytic type of anemia in the presence of free hydrochloric acid in the gastric contents, disease of the liver should be suspected. With pernicious anemia thus essentially ruled out and the other aforementioned causes eliminated by further study, the diagnosis should be considered established. The exact pathologic changes present in the liver could not, of course, be foretold. It could be said only that the hypothetical erythropoietic function of the liver had been disturbed.

Although one could go no further than this, the sign might prove of great practical value in certain cases. For example, in the differential diagnosis of ascites, the hepatic origin would be established and an exploratory laparotomy avoided.

#### SUMMARY

1. An introductory case illustrating the occurrence of macrocytic anemia in cirrhosis of the liver is briefly reported.
2. References from the literature show this to be a widely recognized syndrome.

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25. Jones, N. W., and Joyce, T. M.: Further Remarks on Infections of the Gall Bladder in Relation to Chronic (Pernicious) Anemia, *Am. J. M. Sc.* **173**: 526 (April) 1927.

3. Three cases of disease of the liver are reported in which personal study has confirmed the macrocytic character of the anemia.

4. Twenty-eight cases of hepatic cirrhosis were reviewed from the records of the hospital. Macrocytic anemia was found in five cases, or 18 per cent.

5. The mechanism producing a macrocytic type of anemia is discussed. Disease of the liver is given a place in this mechanism.

6. A sign is suggested which may prove useful in the diagnosis of disease of the liver.



# ALEUKEMIC MYELOSIS

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There are occasional cases of generalized myeloid hyperplasia and metaplasia which are not adequately described by the term myelogenous leukemia. Such cases are usually reported as aleukemic leukemia or aleukemic myelosis. In other groups of cases myeloid hyperplasia or metaplasia may be localized, forming single or multiple tumors within the bone marrow (multiple myeloma of the myeloid type) or extra-medullary tumors (myeloblastomas). We wish to describe several instances of these less common forms of myeloid disease and to discuss their clinical recognition.

Table 1 presents the hematopoietic diseases appearing in the records of the University Hospital for a seventeen year period. The majority of the cases and all except one (case 3) of those reported in detail have been seen in the past eleven years and have been observed by one or by both of us. Necropsy and biopsy studies, for the most part, have been under the direction of Dr. G. H. Hansmann. Those cases in which the data were insufficient to establish a definite diagnosis have been excluded.

Secondary anemias have been excluded, as have the cases of idiopathic hypochromic anemia. Difficulty was encountered in the classification of a group of patients, mostly females, in whom there was an abnormal tendency to bleed, but in whom the attributes of hemorrhagic purpura and of hemophilia were lacking. These were excluded. One patient in whom erythroblasts consistently formed more than half of the nucleated elements in the circulating blood but in whom circulating myelocytes were also numerous has been classified as having leukemic myelosis. Permission for necropsy was not obtained, so that the possibility of erythroblastic anemia (leukemia) could not be excluded. We also studied a group of twelve children who suffered from a fatal hematopoietic disease which we have classified temporarily as sub-leukemic lymphatic leukemia. The children had low or normal total leukocyte counts without young cells, but with a severe neutropenia, laboratory and clinical evidence of purpura haemorrhagica, often some enlargement of the fixed lymphatic tissue and a progressive anemia

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with slight but definite evidence of regeneration and a color index of about unity. Infection, especially about the mouth, was prominent as a terminal event in most instances. Necropsy was obtained in three cases, biopsy of bone marrow in one and biopsy of a lymph node in still another. The lymph node appeared neoplastic (lymphoma), and the bone marrow showed cells of the lymphoid series to the exclusion of myeloid elements. The histologic evidence of leukemia in two of the cases that came to necropsy was not convincing in that "infiltration" of the parenchymatous organs was not marked. In the third case there was marked leukemic "infiltration" of the organs, especially the liver. From clinical and hematologic standpoints, the cases were all alike and resembled closely those reported by Abt<sup>1</sup> and by Hyland.<sup>2</sup>

TABLE 1.—*Hematopoietic Diseases at University Hospital Over Seventeen Year Period*

Condition	Cases	Condition	Cases
Pernicious anemia.....	492	Myelosis, leukemic (chloroma).....	1
Anemia of pregnancy.....	4	Myelosis, aleukemic diffuse.....	4
Chlorosis.....	5	Myelomas, extramedullary.....	2
von Jaksch's anemia.....	3	Multiple myeloma, myeloid type.....	2
Aplastic anemia (benzene poisoning)..	1	Multiple myeloma, plasma cell type...	5
Aplastic anemia (neoarsphenamine)..	1	Monoeytic leukemia.....	3
Aplastic anemia, idiopathic.....	8	Lymphoma:	
Sickle cell anemia.....	1	Lymphocytic type, leukemic.....	86
Banti's syndrome.....	24	Lymphocytic type, subleukemic....	12
Familial hemolytic icterus.....	14	Lymphocytic type, aleukemic.....	24
Acquired hemolytic icterus.....	4	Lymphoblastic type.....	36
Polycythemia vera.....	10	Endothelial type.....	6
Idiopathic neutropenia.....	4	Sclerosing type.....	76
Acute (blast cell) leukemia.....	13	Unclassified (biopsy not obtained)..	36
Hematopoietic tumor (undifferenti- ated), extramedullary.....	2	Benign (?) lymphoma.....	1
Myelosis, leukemic.....	64	Purpura haemorrhagica, idiopathic...	8
		Hemophilla.....	8

The following cases represent all of the instances of proved aleukemic myelosis and multiple myeloma (myeloid type) which we have recognized. Extramedullary myeloid tumors have also been included in this report.

#### REPORT OF CASES

##### CASE 1.—*Leukemic myelosis (aleukemic period induced by irradiation).*

A. D., a white man, aged 59, presented typical manifestations of leukemic myelosis. He was given repeated roentgen treatments over the spleen during a period of two years. A few of the blood counts are given to show the trend of the blood picture. This case is included to show an aleukemic interval such as may develop during irradiation in ordinary leukemic myelosis.

1. Abt, I. A.: A Case of Aleukemic Leukemia with Clinical Symptoms of Plastic Anemia, *M. Clin. North America* 8:427 (Sept.) 1924.

2. Hyland, C. M.: Lymphatic Leukemia Without Leukocytosis, *Am. J. Dis. Child.* 39:59 (Jan.) 1930.

TABLE 2.—*Blood Counts in Case 1*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Neutrophils	Metamyelocytes	Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
1/13/26.....	48	3,760,000	84,000	73	..	23	..	..	..	4	..	..	..	..	..	..
1/18/26.....	50	3,600,000	69,000	48	..	38	..	12	..	2	..	..	..	..	..	..
1/22/26.....	..	3,830,000	21,700	72	..	12	..	10	..	6	..	..	..	..	..	..
2/21/26.....	62	2,940,000	6,800	56	..	13	..	6	..	18	..	..	..	7	..	..
3/ 7/26.....	70	2,600,000	12,000	..	..	..	..	..	..	..	..	..	..	..	..	..
6/15/26.....	60	3,260,000	5,600	80	..	5	..	..	..	12	..	..	..	3	..	..
6/23/26.....	65	4,700,000	10,500	..	..	..	..	..	..	..	..	..	..	..	..	..
11/ 7/26.....	82	4,290,000	47,000	76	..	7	..	5	..	..	..	..	..	12	..	..
11/22/26.....	75	3,600,000	26,700	79	..	13	..	..	..	4	..	..	..	4	..	..
4/ 1/27.....	45	3,760,000	79,000	50	..	15	14	..	..	9	..	..	..	12	..	..
6/16/27.....	..	3,550,000	33,700	38	..	23	21	..	..	2	..	..	..	16	..	..
9/20/27.....	63	3,660,000	47,200	50	..	37	11	..	..	2	..	..	..	..	..	..
1/ 6/28.....	52	3,220,000	35,300	56	..	18	12	..	..	14	..	..	..	..	..	..
2/25/28.....	67	3,280,000	7,800	60	..	4	14	..	..	22	..	..	..	..	..	..

TABLE 3.—*Results of Examination of the Blood in Various Cases*

	Bleeding Time	Clot Retrac- tivity	Con- strictor Test	Platelets, by Volume	Fragility Test	Pro- thrombin Time	Coagula- tion Time	Reticulo- cytes
Average normal	Less than 2 min.	4 + in 4 hrs.	Neg.	0.4 to 0.6 cc. per 100 cc.	Began at 0.44; complete at 0.36	Less than 10 min.	Less than 5 min.	Less than 1 per cent
Case 1	2 min.	4 + in 4 hrs.	Neg.	170,000 per cu.mm.	Began at 0.46; complete at 0.30	Normal	8½ min.	
Case 2	2 min.	1 + in 4 hrs.	Pos.	0.1 cc. per 100 cc.	Began at 0.50; complete at 0.36	Normal	3 min.	
Case 4	22 min.	None in 4 hrs.	Pos.	0.01 cc. per 100 cc.	Began at 0.44; complete at 0.36	Normal	5 min.	3.4 to 7.8 per cent
Case 5	15 min.	Poor in 4 hrs.	Pos.	0.1 cc. per 100 cc.	Began at 0.50; complete at 0.40	Normal	5 min.	10 per cent
Case 6	10 min.	None in 4 hrs.	Pos.	0.05 cc. per 100 cc.	Began at 0.44; complete at 0.34	Normal	4 min.	1.2 per cent
Case 7	2½ min.	4 + in 4 hrs.	Neg.	0.3 cc. per 100 cc.	Began at 0.46; complete at 0.38	Normal	5 min.	
Case 8	1½ min.	None in 4 hrs.	Neg.	1.2 cc. per 100 cc.	Began at 0.50; complete at 0.30	Normal	4 min.	2.4 per cent
Case 9	3 min.	Normal	Pos.	0.31 cc. per 100 cc.	Began at 0.46; complete at 0.44	Normal	3 min.	

CASE 2.—*Leukemic myelosis (spontaneous aleukemic period).*

H. L., a white man, aged 45, was admitted to the University Hospital because of a deep ulceration on the inner surface of the right cheek and enlarged lymph nodes at the angles of the jaw. The other superficial lymph nodes were not remarkable. The liver and spleen were moderately enlarged.

During the course of the disease his temperature was elevated continuously, frequently reaching 103 F. On Aug. 29, 1930, he received a small dose of roentgen rays over the right cheek (140 kilovolts, 5 milliamperes, 50 cm. skin target distance with a filtration of 0.25 mm. copper, and 1 mm. aluminum for fifteen minutes, which gave approximately 120 roentgens). There was temporary subsidence of the swelling. Exophthalmos of the right eye developed later, and the necrotic lesion in the mouth increased in size. The course was progressively downward, and death occurred on October 8.

TABLE 4.—*Blood Counts in Case 2*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Neutrophils	Metamyelocytes	Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
8/17/30.....	68	3,120,000	129,000	14	..	70	6	..	..	10	..	..	..	..	..	..
8/18/30.....	..	..	112,000	20	14	56	..	..	..	3	..	..	..	..	7	..
8/25/30.....	59	3,330,000	53,000	..	..	..	..	..	..	..	..	..	..	..	..	..
8/29/30.....	..	..	64,000	..	..	..	..	..	..	..	..	..	..	..	..	..
8/31/30.....	..	2,550,000	61,500	..	..	..	..	..	..	..	..	..	..	..	..	..
9/ 2/30.....	60	2,600,000	..	84	..	4	..	..	..	12	..	..	..	..	..	..
9/ 7/30.....	60	2,550,000	60,100	..	..	..	..	..	..	..	..	..	..	..	..	..
9/11/30.....	..	..	..	78	1	1	..	..	7	9	..	1	..	3	..	..
9/12/30.....	..	..	..	80	..	..	..	..	..	19	..	..	..	..	1	..
9/14/30.....	..	..	8,200	..	..	..	..	..	..	..	..	..	..	..	..	..
9/17/30.....	..	..	7,100	76	..	..	..	..	..	18	..	5	..	1	..	..
9/19/30.....	35	1,580,000	6,300	76	..	..	..	..	1	18	..	4	..	..	1	..
9/29/30.....	32	1,460,000	9,300	32	8	18	19	..	..	22	..	1	..	..	..	..
10/ 1/30.....	40	1,800,000	15,500	16	2	34	39	..	..	5	..	..	..	4	..	..
10/ 3/30.....	..	..	21,700	13	7	74	3	..	1	2	..	..	..	..	..	..
10/ 5/30.....	..	..	21,300	11	7	35	35	..	1	9	..	..	..	2	..	..
10/ 7/30.....	30	1,560,000	34,000	..	..	..	..	..	..	..	..	..	..	..	..	..
10/18/30.....	..	..	57,000	..	..	63	19	..	..	18	..	..	..	..	..	..

The results of various examinations of the blood are tabulated in table 3. On August 21 the basal metabolic rate was 31 per cent above normal, while on October 3 it was 26 per cent above normal.

It is to be noted that there was a spontaneous remission with a normal white cell count and an absence of immature cells. The polymorphonuclear leukocytes at this time showed more than the normal number of lobulations in their nuclei, i. e., an actual shift to the right. If infection caused the remission, it is peculiar that there should have been a shift to the right.

Necropsy disclosed diffuse myeloid hyperplasia and metaplasia.

CASE 3.—*Aleukemic myelosis, diffuse type.*

F. W., a white man, aged 53, came to the hospital because of weakness of six weeks' duration and edema which had been present for two weeks. The edema first appeared about the eyes, but later became generalized and was followed by some shortness of breath. The heart and lungs were essentially normal. The urine was scanty, varied from 1.016 to 1.020 in specific gravity and contained a few casts and, on one occasion, a trace of albumin. The nonprotein nitrogen of the blood was normal. The formed elements of the blood were not remarkable

(table 5). The patient's condition improved, and he left the hospital after seven weeks. However, he returned six weeks after discharge with the original complaints. At this time the edema was limited to the eyelids, and there was a slight icteric tint to the skin. There were signs of fluid in both pleural cavities. The blood pressure was 108 systolic and 78 diastolic, and the heart was normal. The liver was enlarged, but the spleen was not palpable on admission. The spleen gradually increased in size and for a few days was tender. Gastric analysis revealed an achlorhydria. The blood platelets numbered 355,000 per cubic millimeter. Petechiae and ecchymotic areas appeared, and the edema and dyspnea increased in severity. The patient died in coma ten days after admission. A hemolytic streptococcus grew in a blood culture drawn the day before death.

At necropsy there were many hemorrhages into and beneath the skin, the periosteum of the ribs, the epicardium and the capsules of the kidneys. The spleen was friable and bluish red, weighed 1,830 Gm. and contained numerous infarcts. There were grayish tumors along the coronary arteries and in the kidneys. The liver was enlarged, and the lymph nodes were congested. Bone marrow taken from the midportion of the femur was hyperplastic.

TABLE 5.—*Blood Counts in Case 3*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
8/26/19.....	96	5,070,000	5,320	69	..	..	..	1	..	28	..	2	..	..	..	..
9/23/19.....	..	.....	3,800	68	..	..	..	..	..	29	..	3	..	..	..	..
10/ 3/19.....	70	4,560,000	4,300	71	..	..	..	..	2	22	..	5	..	..	..	..
12/ 1/19.....	65	3,900,000	5,000	70	..	..	..	..	12	20	..	8	..	..	..	..
12/ 9/19.....	70	4,400,000	5,400	62	..	1	..	..	1	28	..	3	..	4	..	1
12/10/19.....	75	4,000,000	9,800	61	..	..	..	1	..	27	..	2	..	4	..	5

Microscopic examination showed infiltration or metaplasia in all organs, the predominant cell being of the myelocytic series. The tumors which could be seen grossly were composed of the same cells. Practically all of the splenic pulp was replaced by rapidly growing tumor tissue showing small areas of hemorrhage. In the liver the central veins, sinusoids and periportal spaces were distended with myeloid cells. There were many hemorrhagic areas in the kidneys as well as extensive collections of myeloid cells within the capillaries. These cells were also found distending the capillaries of all the tissues. The bone marrow was overgrown by myeloid cells.

#### CASE 4.—*Acute myeloid leukemia, diffuse type.*

O. J., a white woman, aged 29, was admitted to the hospital on Sept. 29, 1929, because of profuse vaginal hemorrhage. She had noted increasing pallor and weakness during the preceding month and had had a moderately severe hemorrhage following the extraction of a tooth three weeks before admission. Subsequent to the extraction, the gums became swollen and tender. On admission the skin and mucous membranes were very pale, and although there were ecchymotic areas over the body the hemorrhage from the oral mucous membranes had ceased. The gums were so swollen as to cover entirely some of the teeth. The submaxillary lymph nodes were enlarged, but there was no lymphadenopathy elsewhere nor was the spleen or liver enlarged. Both breasts were enlarged and firm but not nodular or

tender. There was profuse uterine bleeding but otherwise the pelvic organs were normal. By weight of vaginal pads it was found that the loss of blood for twenty-four hours gradually decreased from 500 to 50 Gm. over a period of ten days during which time repeated transfusions were given. Irradiation of the gums caused a rapid subsidence of the swelling. The patient was discharged, but after two weeks at home she returned with markedly swollen gums, numbness of the lower lip and large, irregular, firm nodules in both breasts. A mass developed in the right side of the pelvis and extended upward to the level of the umbilicus, the spleen became palpable, and pain over the bones became prominent. Hemorrhagic neuroretinitis, ecchymotic areas in the skin and profuse uterine hemorrhage developed, and death occurred about four months after the first symptoms had appeared.

Laboratory studies showed normal urine and a negative Wassermann reaction. The basal metabolic rate was 1.4 per cent below normal on October 30, and on November 21 it was 23 per cent above normal. Roentgenograms of the bones were normal except for a defect in the mandible. The blood count was typical of



Fig. 1 (case 4).—Swollen infiltrated gums.

hemorrhagic purpura, as shown in table 3. There was no bilirubinemia. On October 3, the hematocrit reading was 14 per cent, and by the Newcomer method the hemoglobin was 5.3 Gm. Reticulocytes made up 4.8 per cent of the erythrocytes, and polychromatophilia and poikilocytosis were prominent. A clinical diagnosis of aleukemic myelosis was confirmed by a biopsy specimen from the gum.

Some of the neutrophils contained vacuoles, and the granules varied in size and tinctorial properties. The unclassified cells contained a bland, irregular nucleus of a purple tint, and their cytoplasm was pale blue and without granules with Wright's stain. They appeared to be of lymphocytic origin. No typical myelocytes were encountered in the smears, but different observers varied in their ideas as to classification. Two hematologists from other institutions looked at the blood smears. One reported toxic changes in the leukocytes but no immature forms. The other considered some of the cells to be lymphoblasts and thought that there were many abnormal lymphoid cells present.

At necropsy the spleen was found to weigh 310 Gm., and the normal architecture was replaced by a firm, gelatinous, gray, glistening tissue. The right ovary

weighed 350 Gm. and the left, 75 Gm. The enlargement of the ovaries and breasts was due to a friable, gray, nodular, cellular growth with hemorrhagic areas. The bone marrow was reddish gray and glistened. There was no enlargement of the lymph nodes.

Microscopic examination showed that the predominant tumor cell had a large, round, vesicular nucleus with a variable amount of somewhat granular cytoplasm. Some of the cells had distinctly lobulated nuclei and some showed definite granules in their cytoplasm. The ovarian tissue, breasts, spleen and gingiva were so densely infiltrated by these myeloid cells that in places no normal structure could be recognized. The cells were supported by a delicate stroma of fibroblastic tissue, and many of them were in mitosis. In the spleen only a few malpighian corpuscles could be seen, and although the sinusoids remained open they were irregular in outline. A few reticular cells containing erythrocytes were found. The fat of the bone mar-

TABLE 6.—*Blood Counts in Case 4*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
9/30/30.....	50	2,130,000	6,350	..	..	..	..	..	..	..	..	..	..	..	..	..
10/ 2/30.....	40	1,750,000	5,800	44	..	..	..	..	..	15	..	..	..	41	..	..
10/ 3/30.....	30	1,500,000	2,500	..	..	..	..	..	..	..	..	..	..	..	..	..
10/ 4/30.....	30	1,750,000	2,400	30	..	2	..	1	..	15	..	1	..	22	27	2
10/ 6/30.....	25	1,350,000	2,400	..	..	..	..	..	..	..	..	..	..	..	..	..
10/ 7/30.....	23	1,510,000	3,600	45	..	16	..	..	..	23	..	..	..	5	8	3
10/ 9/30.....	30	1,850,000	2,400	32	..	4	..	1	..	6	..	..	..	35	19	3
10/14/30.....	40	2,150,000	2,600	50	..	..	..	..	2	35	..	..	..	9	3	1
10/18/30.....	40	3,000,000	2,800	50	..	..	..	..	..	37	..	..	..	8	5	..
11/12/30.....	..	2,440,000	5,900	55	..	..	..	..	1	27	..	..	..	17	..	..
11/18/30.....	53	2,910,000	5,400	51	..	..	..	1	1	16	..	6	..	16	9	..
11/30/30.....	35	1,970,000	17,600	36	..	15	1	..	2	15	..	2	..	23	3	3
12/ 7/30.....	..	..	..	44	..	1	..	..	..	13	..	..	..	40	..	2
12/10/30.....	53	1,900,000	5,600	..	..	..	..	..	..	..	..	..	..	..	..	..
12/21/30.....	31	1,790,000	5,200	33	..	1	8	2	..	9	..	..	..	25	22	..

row was replaced by dense masses of erythrocytes, and myeloid cells and mitoses were numerous. A hemolytic streptococcus was isolated from the heart's blood at necropsy.

#### CASE 5.—*Aleukemic myelosis, diffuse type.*

H. S., a white woman, aged 22, was admitted to the University Hospital on Dec. 5, 1930. About June 1, when she was five months pregnant, pain developed in the sacral region which became so severe that labor was induced one month later. Although the sacral pain disappeared, she never regained her normal strength, and subsequently pain and swelling of the ankles, knees, fingers, wrists and elbows developed. In September, small white nodules appeared in the skin over the face and neck. These were firm but not tender and were unduly white as from stretching of the overlying skin. Similar nodules appeared over the entire body, but were most numerous on the forearms and legs. The patient had always bruised easily but had never bled profusely. She was brought to the hospital because of extreme weakness and pallor.

The patient was emaciated, and the skin and mucous membranes were pale. The cervical, axillary and inguinal lymph nodes were enlarged, firm and freely movable, but not tender. The liver was enlarged, and the splenic dulness was

increased. Both breasts contained numerous firm nodules which varied from 0.5 to 1 cm. in diameter. They were freely movable and were not attached to the overlying skin or the nipple. The muscles were small, atrophic and tender to pressure. The skin was thickened and inelastic over the entire body and contained small firm nodules which were almost confluent over the forearms, legs, feet and hands. These nodules seemed to arise from the subcutaneous tissue and deep layers of the skin. After a constrictor had been placed about the arm, hemorrhages appeared at the periphery of each nodule. Irradiation (136 kilovolts, 4 milliamperes, 50 cm. skin target distance with a filtration of 3 mm. of aluminum, which gave 200 roentgens in eighteen and a half minutes) was given over a small area on the forearm. The size of the nodules in this area decreased about 75 per cent within seventy-two hours.



Fig. 2 (case 5).—Cutaneous nodules on the forearm and face.

The urine did not contain Bence-Jones protein, but there was a trace of albumin. The Wassermann reaction was negative. The results of several examinations of the blood are recorded in table 3. The blood calcium was 11 mg., the phosphorus 4.08 mg. and the plasma cholesterol 192.3 mg. per hundred cubic centimeters. The basal metabolic rate was 70 and 66 per cent above normal on two successive days but the temperature was 100 F. on each occasion.

Roentgenologic examination of the skeleton showed areas of calcium absorption and some subperiosteal proliferation parallel to the long axis of the bones. Perpendicular spicules were found, particularly at the tendon and muscle attachments on the femora, ischia, pubes, radii and ulnae and in the metacarpals. The lesions in the spine showed more of an osteoblastic type of reaction, but there were also areas of calcium absorption. The cranial bones showed multiple pinpoint areas of decalcification.



The thickened inelastic and tightly drawn skin, as well as the atrophic and tender muscles, suggested a diagnosis of dermatomyositis, but this was obviously untenable in the face of the other findings.

The roentgenologic changes in the bones, the nodules on the skin and breast and even the microscopic appearance of the skin and a lymph node removed for biopsy were suggestive of carcinomatosis. However, the splenomegaly (which is rare in carcinoma), the multiple tumors of the breast, the marked increase in the consumption of oxygen and the almost miraculous response of the cutaneous tumors to

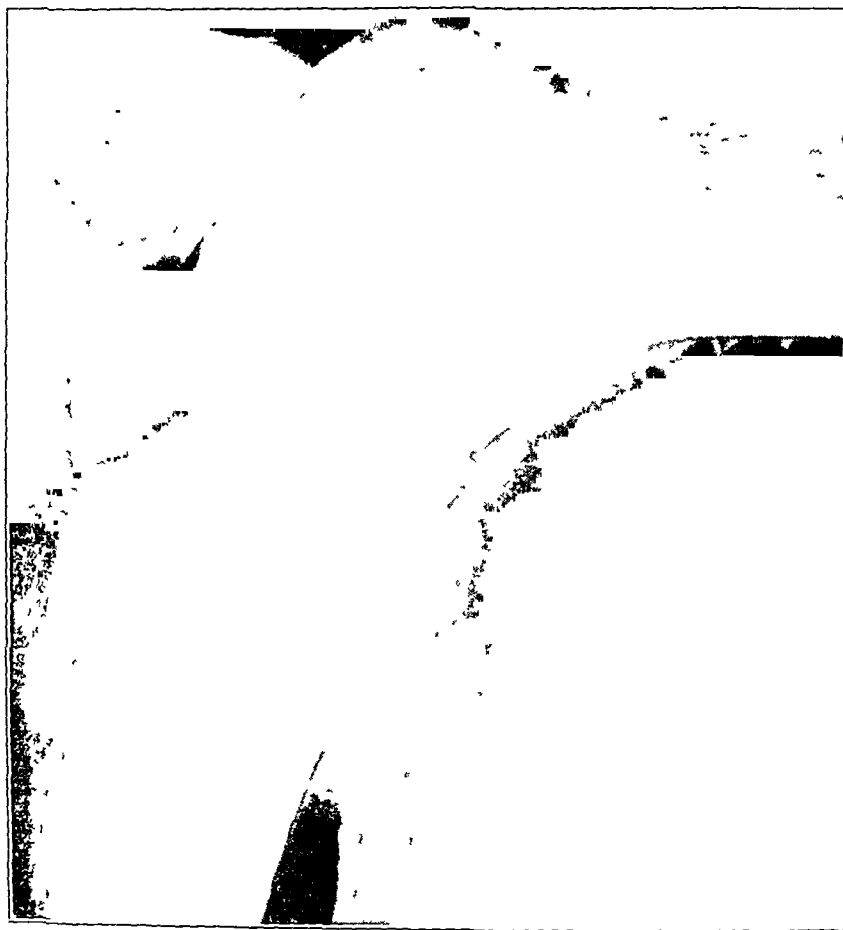


Fig. 3 (case 5) —Perpendicular spicules of bone at the lower end of the femur.

erration led to a clinical diagnosis of a hematopoietic disease. Necropsy left no doubts as to the correctness of this impression.

The course of the patient's condition was progressively downward, and she died at her home on December 28.

Necropsy was performed by Dr. A. B. Konwaler of Davenport, Iowa, who turned the tissue over to us for study. The myocardium was pale, and a small white nodule was noted beneath the epicardium of the left ventricle. The pericardium was thickened and adherent to the pleura and several hemorrhagic lymph nodes were attached to it. The mediastinal lymph nodes were enlarged. The normal architecture was lost, the hilus obliterated and the tissue had the grayish, granular appearance of great cellularity. The spleen was enlarged, grayish and friable, and contained one large scar. The liver was enlarged, light in color and friable, and contained

numerous round nodules, some of which were white and others hemorrhagic. The largest nodule measured 4 cm. in diameter. The kidneys were large, and the capsule stripped easily, leaving a nodular hemorrhagic surface. They were pale on cut section and contained scattered hemorrhagic areas.

The abdominal and retroperitoneal nodes were greatly enlarged and loosely matted together. They were firm and on cut section presented a smooth gray surface with scattered areas of hemorrhage. The periosteum of the ribs was thickened and that of the femur was roughened and contained round, white, dense areas and also some yellowish mottling. The bone marrow of the femur was grayish red.

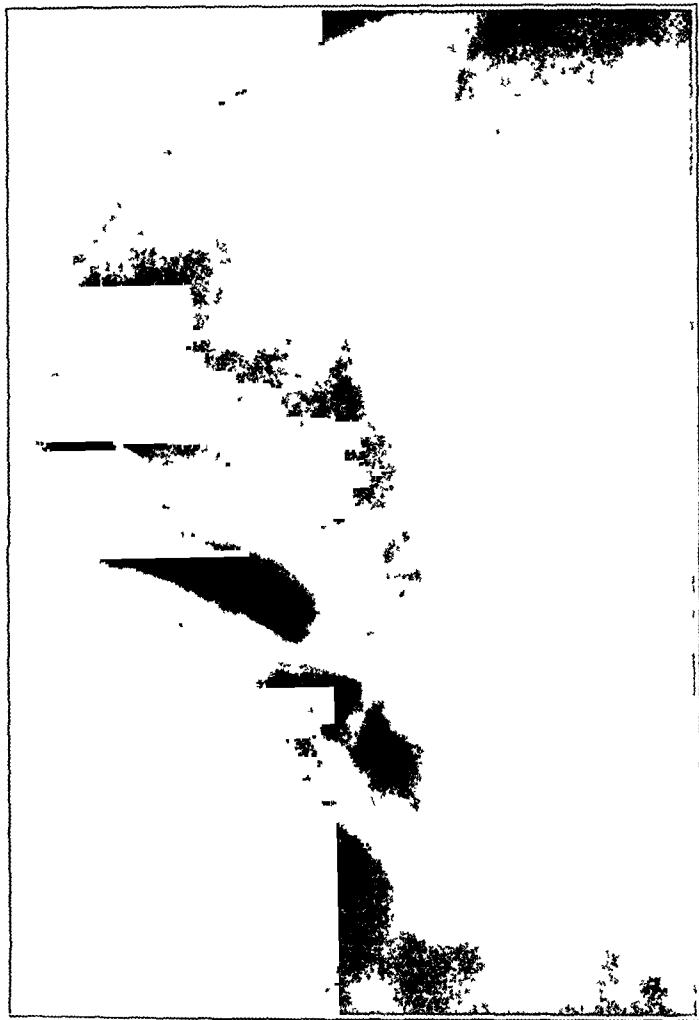


Fig. 4 (case 5).—A portion of the skull showing the multiple pinpoint areas of decalcification.

Microscopic examination showed the "infiltrating" cells which appeared in nearly every tissue to be from two to three times the diameter of an erythrocyte. The nuclei were round, oval or lobulated, and many contained nucleoli. The cells had an abundant cytoplasm which was usually molded by their close apposition. In some, the cytoplasm was stippled with fine granules, part of which were eosinophilic. A few cells with basophilic granules were found. Mitotic figures were numerous, and some cells were multinucleated.

The heart showed a moderate perivascular infiltration by cells of the type described, and the nodule described grossly consisted of densely packed cells infiltrating the cardiac muscle. Sections of the lungs showed no infiltration.

The spleen was, for the most part, packed with the large myeloid cells, and only an occasional adult neutrophil or lymphocyte was seen. A few multinucleated cells and a few mitotic figures were seen. An occasional nucleated erythrocyte was found.

Lesions of two types were found in the liver. In the first there was a nodular mass of hematopoietic cells growing so as to compress the liver cords and produce degenerative changes in the hepatic cells. The second type of lesion consisted of a dense infiltration of the sinusoids of the liver, and in these areas more adult neutrophils were present.

The kidneys showed a marked infiltration by hematopoietic cells. A similar infiltration was present in the ovary, uterus, trachea and other structures. In the breasts there was a marked fibroblastic reaction, which caused the cells to form into cords and layers. In the lymph nodes the follicles were compressed by the hematopoietic cells, and multinucleated cells were frequent.

In the skin these cells were collected in groups and cords and had invaded the deeper layers of the skin and subcutaneous fat.

TABLE 7.—*Blood Counts in Case 5*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
12/ 5/30.....	39	2,370,000	6,840	13	1	..	11	..	1	1	43	..	..	..	4	..	26
12/ 6/30.....	..	..	..	6	11	5	8	2	1	5	32	..	1	..	6	5	18
12/13/30.....	34	2,020,000	8,100	4	3	9	6	1	2	3	4	..	..	..	18	25	25
12/18/30.....	33	2,150,000	11,600	5	8	5	17	..	1	3	10	1	..	..	9	15	26

The cortex of the bone showed marked sclerosis, while the marrow spaces were rich in cells. There was infiltration of the periosteum of the ribs, and the marrow of both the ribs and long bones was filled with the myeloid cells. The marrow of the long bones contained more erythrocytes and erythroblasts than that of the ribs.

#### CASE 6.—*Alcukemic myelosis, diffuse type.*

J. W., a white girl, aged 11 years, was brought to the University Hospital on Jan. 15, 1931, because of anemia, weakness and loss of weight which began five months prior to her admission. During September, 1930, she had an attack of vomiting, diarrhea and fever of three days' duration, following which she received four blood transfusions. Following the last transfusion, she had a fever and severe hemorrhages from the nose. She had attacks of pain and swelling which migrated from one joint to another until practically every joint in the body had been involved.

Examination revealed marked pallor, weakness, bloody crusts in the nose and excoriations of the soft palate. The anterior cervical, axillary and inguinal lymph nodes were palpable. There was dulness with suppression of breath sounds at the base of the right lung. The liver was not palpable, but the spleen was tender and extended 3 cm. below the costal margin. The ankles and wrists were tender and motion was painful. She became worse in spite of repeated blood transfusions, and hemorrhages from various areas became a prominent feature. She died on February 2. Permission for necropsy was not obtained.

The urine was normal. The Wassermann and tuberculin tests were negative. Before admission the leukocyte count had varied from 1,200 to 4,000 per cubic millimeter, and there were from 8 to 11 nucleated erythrocytes to every 100 leukocytes. The blood cultures remained sterile. The results of the blood studies are recorded in table 3. The blood cholesterol was below 10 mg. per hundred cubic centimeters. The blood calcium was 9.7 mg. and the phosphorus 3.9 mg. per hundred cubic centimeters.

Roentgenograms of the skeleton showed evidence of rarefaction of the distal ends of the femora, tibiae and left radius and ulna. Similar changes were seen in the metacarpals and phalanges. No disturbance of the architecture of the bone was present, and the trabeculations were not increased. There was some thinning of the cranial vault, with a generalized loss of calcium from the pelvis.

A cervical lymph node was removed. There was a hemorrhagic area beneath the capsule, and on cut section the surface was smooth, gray and granular. The

TABLE 8.—*Blood Counts in Case 6*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
12/ 8/30.....	22	1,500,000	9,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/ 9/30.....	32	1,960,000	4,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/10/30.....	34	1,900,000	3,500	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/11/30.....	32	1,880,000	3,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/12/30.....	30	1,850,000	2,500	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/13/30.....	34	1,500,000	3,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/15/30.....	20	1,490,000	4,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/16/30.....	22	1,400,000	3,500	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/17/30.....	28	2,000,000	4,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/21/30.....	30	2,000,000	3,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/22/30.....	34	1,500,000	2,500	12	15	..	9	8	..	2	11	..	16	13	..	6	7
1/16/31.....	35	1,240,000	16,000	7	8	..	10	12	1	..	35	5	4	14	..	3	1
1/19/31.....	..	.....	6,900	..	..	..	..	..	..	..	..	..	..	..	..	..	..
1/23/31.....	45	2,840,000	7,400	7	19	..	18	5	1	4	4	1	7	25	..	7	2
1/25/31.....	40	2,500,000	5,500	19	29	..	14	5	2	3	3	1	..	18	..	6	..
2/ 1/31.....	35	1,950,000	2,600	..	..	..	..	..	..	..	..	..	..	..	..	..	..

normal architecture could not be distinguished grossly or histologically. The sinuses were filled with cells, and no germinal centers were visible. The cytoplasm of the predominant cell contained granules, and the nuclei were large and vesicular. Few of the cells contained polymorphic nuclei. Many mitotic figures were present, and there were numerous eosinophils. The tissue was made up of hematopoietic cells, most of which appeared to be very young, and the granules suggested their myelocytic nature. The pathologic diagnosis from the biopsy specimen was myelosis.

Examinations of the blood prior to this patient's admission to the University Hospital were made by Dr. H. W. Rathe. Blood smears for this period were examined by one of us and were found to contain numerous erythroblasts but no other young cells and few abnormal leukocytes. Actual differential counts were not made. In this case, also, there were no definite myelocytes, since the cells which resembled myelocytes in other respects were nongranular. The "blast cells" were also of questionable classification in that they did not appear to contain nucleoli. The leukocytes were similar to those in case 4.

## CASE 7.—Multiple myeloma, myeloid type?; aleukemic myelosis, diffuse type?

I. M., a white woman, aged 52, was admitted to the University Hospital on Aug. 24, 1932, because of pain in the lower part of the back and loss of strength. The weakness was first noticed about ten months prior to her admission and gradually progressed until it became the most prominent symptom. Six months prior to admission pain developed over the upper part of the chest which seemed to migrate to the back and persisted in two areas just medial to the scapulae. The patient was forced to be extremely careful when bending over, but continued with her housework until two months prior to her admission, when she fell and was unable to arise because of pain in the lumbar region. The following morning she had a severe cramp in the muscles of the lower part of the back and was unable to straighten up. This pain and muscle spasm gradually subsided during the next two months, but her weakness became so extreme that she was confined to her bed.

The patient was very pale but not icteric. The skin was dry, and there was evidence of much loss of weight. There was no lymphadenopathy, although the

TABLE 9.—Blood Counts in Case 7

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
8/24/32.....	44	1,710,000	6,950	36	12	..	..	..	..	1	44	..	2	..	..	5	..
9/10/32.....	32	1,560,000	6,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
9/19/32.....	21	1,220,000	5,100	..	..	..	..	..	..	..	..	..	..	..	..	..	..
9/21/32.....	..	.....	.....	32	8	..	..	..	..	1	42	..	8	3	1	5	..
9/22/32.....	25	1,550,000	6,300	30	12	..	..	..	..	1	43	..	8	1	1	4	..
10/ 3/32.....	26	1,450,000	5,050	44	4	..	..	1	..	..	38	1	7	..	..	4	..
10/ 7/32.....	30	1,680,000	.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..
10/10/32.....	35	2,240,000	5,300	..	..	..	..	..	..	..	..	..	..	..	..	..	..
10/17/32.....	39	2,260,000	4,500	30	27	1	..	..	..	..	16	..	2	14	..	10	..

spleen extended 3 cm. below the costal margin and the edge of the liver was palpable. The lungs were clear, and the heart normal except for a hemic murmur. The blood pressure was 144 systolic and 72 diastolic. There was slight tenderness over the lumbar spine and a tender thickening could be felt over the sixth rib on the left in the anterior axillary line. There was no other bony tenderness.

Roentgenograms of the skeletal system revealed multiple, rounded, sharply defined osteolytic areas involving the skull, ribs, pelvis, second lumbar vertebra, left humerus and femora. Roentgenologic examinations of the gastro-enteric and genito-urinary tracts gave negative results. The urine contained some albumin and a few granular casts. Bence-Jones protein was found in the urine on one occasion. The Wassermann reaction of the blood was twice anticomplementary and the Kahn test was negative, as was the Wassermann reaction of the spinal fluid. The van den Bergh test was negative on two occasions. The specific gravity of the urine varied from 1.009 to 1.013, and the urinary output during the night slightly exceeded that during the day. The excretion of dye was 10 per cent in two hours, and the urea clearance was 26 per cent of normal, but there was no retention of nonprotein nitrogen in the blood. The basal metabolic rate was 25.7, 15.6, 17.5 and 21 per cent above normal on different days.

At different times and by different chemists the blood calcium was found to be 16.7, 17.1 and 16 mg. per hundred cubic centimeters. The serum calcium was 15 mg. and the spinal fluid calcium, 6.5 mg. Urinary calcium for a twenty-four hour period was 768 mg., while the value for phosphorus was 589 mg. The blood phosphorus (inorganic) was also determined by three chemists, the values being 2.8, 2.66 and 3.1 mg. The serum phosphorus was 3.5 and 3.8 mg. The total phosphorus of whole blood was 26.7 mg. and of the serum, 10.4 mg. The hematocrit reading at the time of these determinations was 15 per cent. The serum protein was found to be 12.3 per cent (albumin, 1.5 and globulin 10.8 per cent),

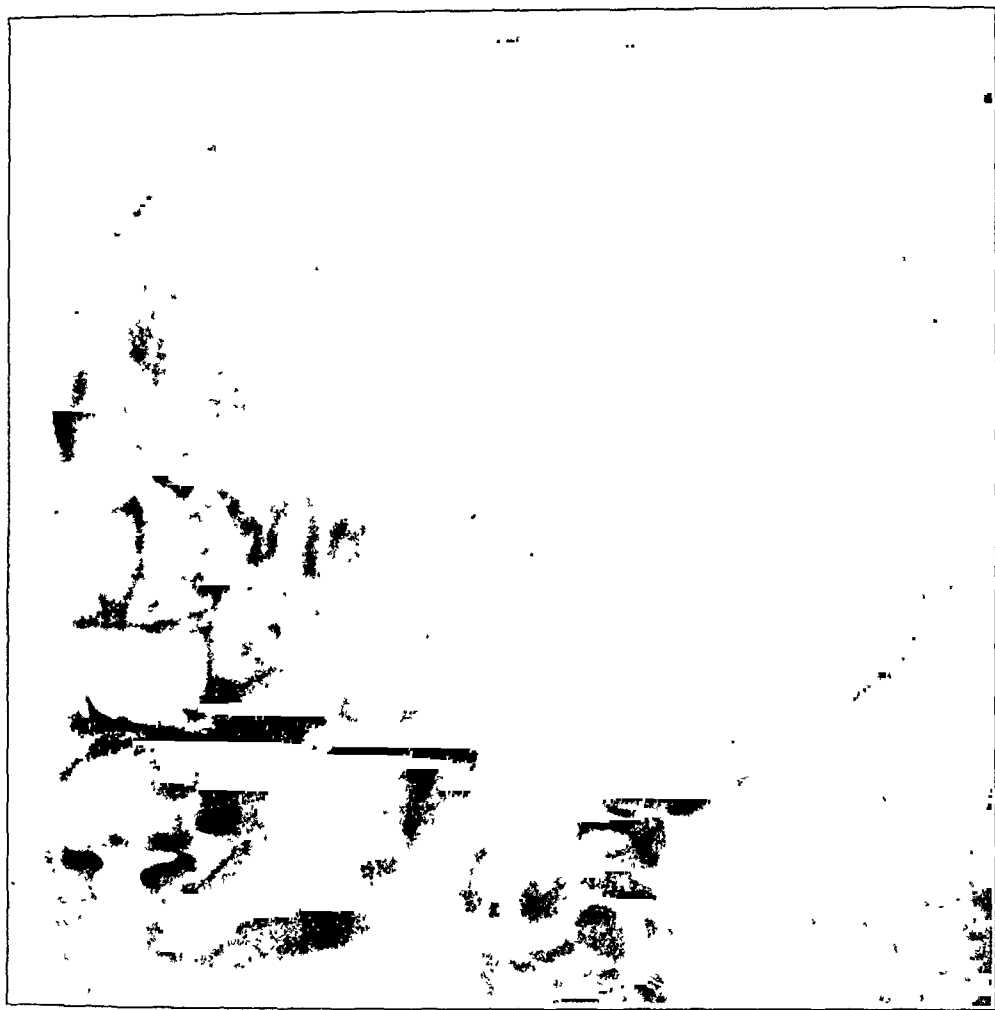


Fig. 5 (case 7).—Multiple rounded osteolytic areas in the skull.

and a week later it was 10.3 per cent (albumin 1.4 and globulin 8.9 per cent). Another determination by another laboratory after a lapse of a week showed plasma protein 7.43 per cent (fibrinogen 0.51, albumin 1.56 and globulin 5.36 per cent). The serum cholesterol was found to be 82 and 62 mg. per hundred cubic centimeters on two occasions, while the plasma cholesterol was 113.6 mg. a week later.

A biopsy was made from one of the lesions in the skull. There was a clean-cut lytic lesion which had penetrated neither the outer nor the inner table completely. The bone about the lesion appeared normal. The soft tissue removed was gray, finely granular and friable and appeared to be extremely cellular on

gross examination. Microscopic examination revealed the tissue to be very cellular, the predominating cell being moderately large with a light-staining, round, vesicular nucleus which was notched in some cells. The cytoplasm was pink (hematoxylin-eosin stain) and was not abundant. Several mycotic figures and a few megakaryocytes were seen. The diagnosis was the myeloid type of multiple myeloma.

The patient was discharged from the hospital at the request of relatives.

CASE 8.—*Multiple myeloma, myeloid type.*

C. N., a white woman, aged 63, was admitted to the University Hospital on Dec. 16, 1930, because of severe pain in the right shoulder and left hip. This pain began in the left hip in the summer of 1929 and was sharp and shooting, but did not radiate, and the area had never been discolored or swollen. A similar pain appeared in the right shoulder and was present even with the part at rest.

There was severe pain in the right shoulder on the slightest motion, but there was no swelling or crepitation, and passive motion was restricted only because

TABLE 10.—*Blood Counts in Case 8*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
12/16/30.....	69	4,000,000	11,550	63	8	..	1	..	..	4	17	..	5	1	1	..	..
12/31/30.....	..	.....	15,800	..	..	..	..	..	..	..	..	..	..	..	..	..	..
1/ 7/31.....	..	.....	12,400	..	..	..	..	..	..	..	..	..	..	..	..	..	..
1 30/31.....	56	3,920,000	12,600	45	30	..	1	..	..	1	16	..	3	3	1	..	..
2 7/31.....	61	3,920,000	8,650	37	26	..	..	..	..	2	..	..	12	23	..	..	..
3 7/31.....	59	3,930,000	5,850	67	4	..	..	..	..	8	..	..	10	7	4	..	..

of the pain. The reflexes were normal, but there was some atrophy of the intrinsic muscles of the right hand. The left thigh was held flexed and adducted, and there was severe pain on motion but no crepitation. There was some pain over the adductor muscles. The spleen and lymph nodes were not enlarged.

The urine showed a trace of albumin, but no Bence-Jones protein could be found. The Wassermann reaction was negative. The results of examinations of the blood are shown in table 3. The blood calcium was 8.6 mg. and the blood phosphorus 4.3 mg. per hundred cubic centimeters. The basal metabolic rate was found to be 7.9 and 7.6 per cent below normal on two occasions. The blood cholesterol was 94.7 mg. per hundred cubic centimeters. Pelvic examination and roentgen examinations of the gastro-enteric and urinary tracts gave negative results. Roentgenograms of the right scapula showed a large area of destruction, purely osteolytic in type, and there were similar lesions in several of the ribs. There were multiple large areas of destruction in both sides of the pelvis, in the lesser trochanter on the right femur and in the greater trochanter on the left femur. Roentgenograms taken one year previously showed a less extensive destructive lesion involving the greater trochanter on the left.

The pain persisted in spite of repeated irradiation over the involved areas. The patient became progressively weaker and died on March 22, 1931. Permission for necropsy was refused.

A biopsy was made from the lesion in the right scapula. This showed dense fibrous tissue with areas composed of large pale-staining cells with a granular cytoplasm and vesicular nuclei. Some of these cells were in mitosis. There were many lymphocytes and a striking number of eosinophils in the lesion, but the predominant cell was of myeloid origin.

*Comment.*—Although absolute proof is wanting, it seems fair to infer that in this case the myelosis was of the localized form. The long duration, the localized bony defects and the almost complete lack of abnormalities in the peripheral blood all strongly suggest that the bone marrow was not diffusely involved.

This process is, of course, closely related to the ordinary type of multiple myeloma of the plasma cell type.

CASE 9.—*Myeloma, extramedullary.*

D. B., a white girl, aged 16, was admitted to the University Hospital on Jan. 27, 1932, because of a protrusion of the right eye. In September, 1931, she first noticed some swelling of the right cheek which receded after the application of heat. She had no further trouble until three weeks prior to her admission, when exophthalmos of the right eye was noticed. This gradually increased, but there was no visual disturbance or pain associated with the protrusion.

There was a marked exophthalmos of the right eye, but the ocular motions were normal. The right eye was distinctly higher than the left, and a hard mass was felt at the junction of the inferior with the lateral rim of the orbit. The remainder of the physical examination gave negative results.

Roentgenologic examination of the orbital region showed a small tumor in the soft tissue, but there was no evident defect in the bone.

A biopsy was made from the tumor mass, and the pathologic report stated that this consisted of fibrous tissue which was infiltrated with lymphocytes, plasma cells and endothelial cells without any regularity of distribution. There were also many cells with a polymorphic type of nucleus, and these appeared to belong to the myelocytic series. Myeloid cells were present in such numbers that it was felt that the tumor was of myeloblastic origin, and the diagnosis of myeloblastoma was made.

Roentgen therapy was applied to the region of the tumor for a period of twelve days during which the patient received 2,400 roentgens. Following this the tumor was removed surgically, and radium needles were inserted at the time of operation.

During the course of treatment she complained of pain in the right knee and ankle, and a purpuric rash appeared over both legs extending up to the trunk. There was a slight swelling of both the right knee and ankle without redness or local heat, although the joints were extremely painful. The patient had experienced an identical episode about one year previously.

The urine showed an occasional finely granular cast and a trace of albumin. The Wassermann reaction was negative. Special blood tests are shown in table 3.

Two other children were encountered with clinical manifestations almost identical to those in this case. Biopsy of a specimen from the orbital tumor was made in each instance, and both growths were found to be hematopoietic tumors, but myeloid cells did not predominate in either. Lymphoid and undifferentiated cells predominated in one, and in the other the tumor cells were undifferentiated,



but a myelophthisic anemia and changes in the roentgenograms of the pelvic bones indicated that the bone marrow was being invaded.

CASE 10.—*Myeloma, extramedullary.*

I. C., a white man, aged 36, was admitted to the University Hospital on Jan. 15, 1926, because of loss of strength and the presence of a nodule on the left wrist. The illness began with pain in the right arm in March, 1923, and in December, 1923, the arm became weak and numb. In March, 1924, a nodule appeared at the right elbow and another at the right wrist. These were not painful except after injury. The tumors were removed in September, 1924, but recurred, and in January, 1925, were again removed together with a piece of bone from the right wrist. In June, 1925, a similar nodule appeared on the left wrist. He had noticed some loss of strength during the year 1925.

TABLE 11.—*Blood Counts in Case 9*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
3/ 9/32.....	80	4,140,000	8,200	68	6	..	2	..	..	4	9	..	6	2	..	3	..
3/11/32.....	85	4,190,000	12,400	73	4	..	..	..	..	2	17	..	4	..	..	..	..

TABLE 12.—*Blood Counts in Case 10*

Date	Hemo- globin	Erythro- cytes	Leuko- cytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
1/15/26.....	80	2,660,000	2,600	74	..	..	..	..	..	..	26	..	..	..	..	..	..
1/18/26.....	59	3,250,000	.....	60	..	..	..	..	..	..	22	..	18	..	..	..	..
1/24/26.....	60	3,480,000	14,400	..	..	..	..	..	..	..	..	..	..	..	..	..	..

The results of general physical examination were not remarkable. There were linear scars over the right elbow and wrist and there was atrophy of the intrinsic muscles of both hands. On the radial side of the left wrist was a spindle-shaped nodule 5 by 2.5 cm. This was tender, and pain radiated both distally and proximally from the growth. The mass was not attached to the underlying structures except at the two poles, and the skin was movable over the tumor mass. There was a loss of pain and thermal sensations and a partial paresthesia on the radial aspect of the left hand.

The tumor was removed surgically and was found to follow the course of a superficial nerve. Fever developed the second day after the operation, and the patient died in coma on January 24.

Roentgen examination of the skeletal system gave negative results. The Wassermann reaction was negative. A lumbar puncture, the day after admission, showed 13 cells per cubic millimeter and a 1+ globulin reaction. The urine was normal.

Examination of the brain at necropsy revealed an acute streptococcic encephalitis. The heart, lungs, liver and kidneys were normal on both gross and microscopic examination. The spleen weighed 350 Gm. The color was more of a bluish tint than normal, and the spleen was soft in consistency. On cut section the pulp appeared cellular, and the malpighian bodies were more prominent than normal. Microscopic examination revealed the pulp to be infiltrated and the venous sinuses filled with cells of the granulocytic series, mainly myelocytes and myeloblasts.

The lymph nodes were not enlarged, and on microscopic examination only a healed tuberculous lesion was found in the mediastinal glands. The bone marrow was not examined.

The tumor removed surgically was not encapsulated and appeared grayish, opaque and very cellular. The stroma was made up chiefly of blood vessels and supporting connective tissue. In the majority of the cells the nuclei were deep-staining and were frequently bilobed; a few were multinucleated. The cytoplasm was eosinophilic with hematoxylin-eosin. It was evidently of bone marrow origin, and the pathologist's diagnosis was myeloblastoma.

#### COMMENT

Cases of true aleukemic myelosis are not numerous in the American literature, but the frequency of their actual occurrence can best be adjudged from studies of the type presented in table 1. About 5 per cent of our cases of diffuse myelosis were permanently aleukemic. Most physicians seem to regard aleukemic myelosis as an obscure form of hematopoietic disease which can be diagnosed only at necropsy. Certainly acceptable criteria for an accurate clinical diagnosis have not been established.

We have accepted the term "myelosis" because it refers to a more fundamental hematopoietic change than does "leukemia," and at the same time avoids the necessity for using such an inherently contradictory term as "aleukemic leukemia."

Two cases of tumors of the bone marrow, as well as two cases of extramedullary tumors composed of myeloid cells are included in this series. The growths in the former two cases are classified as multiple myelomas (myeloid type) because they appear to have more in common with ordinary multiple myeloma of the plasma cell type than with the diffuse forms of myelosis. The extramedullary myeloid tumors resembled the bone marrow type histologically, but the clinical manifestation differed. The latter have been called myelomas.

#### DIFFUSE ALEUKEMIC MYELOSIS

The relationship between permanently aleukemic myelosis and either spontaneous or induced aleukemic periods in leukemic myelosis is not clear. In spite of more or less plausible theories, the actual explanation for the transfer of cells from the fixed hematopoietic tissue to the cir-

culating blood has never been discovered.<sup>3</sup> It is possible that the aleukemic period in case 1 resulted from rather intensive irradiation of the spleen. The skeleton was not irradiated, so that the effect on the bone marrow must have been indirect. It is almost inconceivable, however, that the small amount of irradiation administered to the right cheek in case 2 could have influenced the development of the aleukemic period which followed.

Aleukemic and leukemic myelosis present similar histologic changes.<sup>4</sup> In the aleukemic cases reported by Pinkerton<sup>4b</sup> the leukemic infiltration was quantitatively somewhat less than in ordinary leukemic myelosis. In our cases 3, 4 and 5 the gross and microscopic appearance of the bone marrow and parenchymatous organs did not differ either qualitatively or quantitatively from the appearance in the leukemic form. Clinically, however, there are differences in these two forms of diffuse myelosis even though the differences may not be of fundamental importance. The aleukemic form of myelosis is often more rapidly fatal than the leukemic form, the associated anemia is often more marked and the likelihood of secondary hemorrhagic purpura is greater, but the aleukemic form is of special interest, mainly because it presents certain definite diagnostic difficulties.

*Changes in the Formed Elements of the Peripheral Blood in Diffuse Aleukemic Myelosis.*—In true aleukemic myelosis not only is there an absence of leukocythemia but the differential formula also approaches the normal.<sup>5</sup> In our own cases the degree of abnormality of the blood smear was more or less dependent on the thoroughness with which it was scrutinized from day to day. Certainly a diagnosis could not be made from the blood smear alone in these cases, and some of the stained films might pass as normal on a casual examination. However, to call the blood smears in our cases of diffuse aleukemic myelosis absolutely and consistently normal would be to overstate the facts. One or more of the following abnormalities were encountered in the smears from each of the cases: a leukopenia, a shift to the left in the granulocytes to include a few metamyelocytes and an occasional questionable myelocyte, an abnormal number of basket cells or naked nuclei, bizarre cells which we were unable to classify, occasional erythroblasts or a thrombocytopenia. It is realized, of course, that none of these changes are in any

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3. Isaac, R.: The Physiologic Histology of Bone Marrow, *Folia haemat.* **40**:395, 1930. Doan, C. A.: The Neutropenic State, *J. A. M. A.* **99**:194 (July 16) 1932.

4. (a) Jaffe, R. H.: Aleukemia Myelosis, *Arch. Path.* **3**:56 (Jan.) 1927. (b) Pinkerton, H.: Aleukemic Leukemia and Atypical Leukemoid Conditions, *Arch. Path.* **7**:567 (April) 1929.

5. Mosse, M.: Zur Geschichte der "aleukämischen Myelose," *Centralbl. f. allg. Path. u. path. Anat.* **50**:337, 1931. Jaffe.<sup>4a</sup>

way specific for aleukemic myelosis, since the same changes may be seen in metastatic tumors involving bone marrow,<sup>6</sup> in osteosclerosis<sup>6</sup> and in sepsis.<sup>7</sup>

Anemia unexplained by either hemorrhage or hemolysis is a prominent feature in the diffuse form of aleukemic myelosis. We know of no explanation for the fact that the anemia in aleukemic myelosis may be more profound and may develop more rapidly than that of the leukemic form. Hemorrhage from the uterus contributed generously to the anemia in case 4. However, there was no excess bleeding in case 5, and in case 6 the anemia was grave before the nasal hemorrhages occurred. The anemia is not aplastic, as evidenced by the increase in reticulocytes. In this form of acute myelophthisic anemia the color index may be above unity, perhaps because there is no shortage of materials for the production of hemoglobin, while there is a paucity of space in which the stroma for new cells may develop. Confusion might occur between aleukemic myelosis and pernicious anemia because of the high color index, the leukopenia and the anemia which are common to both diseases.

The thrombocytes were greatly decreased in our cases of diffuse aleukemic myelosis. This may have been on a myelophthisic basis, but an increase in platelets is found throughout most of the course in leukemic myelosis, and the crowding appears to be equally great in both diseases. The regularity and diagnostic importance of these changes in platelets can be determined only by the study of more cases.

The results of further blood studies are shown in table 3. It is apparent from these studies that the laboratory tests for purpura haemorrhagica (long bleeding time, nonretractile clot, positive arm band test and thrombocytopenia) were positive in the three cases of diffuse aleukemic myelosis in which they were done. In this respect the aleukemic differs from the leukemic form of myelosis. Spontaneous ecchymoses and petechiae occurred in all three cases. Experiences such as these have led us to formulate for ourselves certain rigid criteria which must be fulfilled before we advise splenectomy for purpura haemorrhagica. We do not advise splenectomy unless the four laboratory tests previously mentioned are positive in a case in which there is a history of remissions and in which all hematopoietic diseases which lead to secondary purpura haemorrhagica have been excluded. In the cases of idiopathic purpura haemorrhagica which we have observed, remissions were induced relatively easily by transfusion, but this was not true of the cases of secondary hemorrhagic purpuras.

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6. Mavros, A.: Aleukämische, besser "nichtleukämische" Myelose mit Osteosklerose, *Folia haemat.* **43**:323, 1931.

7. Krumbhaar, E. B.: Leukemoid Blood Pictures in Various Clinical Conditions, *Am. J. M. Sc.* **172**:519, 1926.

*Roentgenologic Findings.*—Roentgenograms were of considerable value in the diagnosis of our cases. Case 4 showed an area of calcium absorption in the mandible. In case 5 there were widespread proliferative as well as some osteolytic changes in the skeleton, and a less marked loss of calcium was a feature in case 6. The roentgenologic changes in diffuse aleukemic myelosis might be confused with those of metastatic carcinoma, multiple myeloma of any type or lymphoma with metastases to the bone. The changes in the bone in hyperparathyroidism may be simulated to some degree in diffuse aleukemic myelosis.

*Consumption of Oxygen.*—The consumption of oxygen is usually increased at some time during the course in all types of leukemia. Case 4 (basal metabolic rate,  $-1.4$  and  $+23$  per cent) and case 5 (basal metabolic rate  $+66$  and  $+70$  per cent) tend to show that aleukemic myelosis is no exception to the general rule.<sup>8</sup> If the increase in metabolism proves to be more marked in aleukemic myelosis than in metastatic tumors of the bone marrow (as it has in our experience), it will, of course, be an aid in the clinical diagnosis of the disease.

*Biopsy.*—It is possible that we were unusually fortunate in having suitable biopsy material present itself in our cases. In case 4 material was removed from the margin of the gums; in case 5 from the skin and a lymph node, and in case 6 from a lymph node. Had not these more available materials presented themselves, we should have taken bone marrow (as in cases 7 and 8)—a procedure which we have found to be relatively simple and harmless. The demonstration of hyperplastic gray tissue in areas which are normally fatty in the adult is an important step in establishing a diagnosis of aleukemic myelosis. Microscopic studies should be done by the method of Isaacs<sup>9</sup> as well as by means of sections.

*Other Less Constant Symptoms and Observations.*—Manifestations in the joints not unlike those seen in rheumatic fever occurred in cases 5 and 6. One of us (Dr. Baldrige<sup>10</sup>) previously reported a series of cases of lymphatic leukemia in which 63 per cent of the patients under 21 years of age showed similar symptoms in the joints. It is regrettable that the nature of the changes in the joints could not have been investigated at necropsy.

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8. Baldrige, C. W., and Barer, A.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: II. In Leukemia, *Arch. Int. Med.* **51**:589 (April) 1933.

9. Isaacs, R.: Alterations of Tissue Cells in the Blood Stream, *Science* **68**: 547, 1928.

10. Baldrige, C. W., and Awe, C. D.: Lymphoma, *Arch. Int. Med.* **45**:161 (Feb.) 1930.

Tumefaction of the gums and numbness of the chin, such as occurred in case 4, are not rare in myelosis or in monocytic leukemia, but are uncommon in other dyscrasias of the blood. Areas of calcium absorption from the mandible like that seen in case 4 are at times demonstrable in leukemic myelosis. Either of these findings should cause the physician or dentist to be on his guard, since the extraction of teeth may be a fatal error in chronic leukemia and is rarely, if ever, justified in acute exacerbations of the chronic forms or in acute blast cell leukemia.

The urine in cases 4, 5 and 6 was examined for Bence-Jones protein with negative results. In cases 5 and 6 in which the roentgen changes in the bones were extensive enough to suggest a metabolic disturbance such as hyperparathyroidism, the calcium and phosphorus of the blood were normal. The calcium and phosphorus balances were not determined. We know of no explanation for the extremely low plasma cholesterol in case 6.

Terminal or postmortem blood cultures yielded *Streptococcus haemolyticus* in cases 3 and 4 and *Staphylococcus albus* in cases 5 and 6. These instances of septicemia appeared to be of the ordinary terminal variety. The exact degree of hyperplasia, metaplasia and anaplasia which distinguishes primary hematopoietic disease from response to infection may be a matter of personal opinion in borderline cases. The hyperplasia of the bone marrow which was associated with absorption of cancellous bone and the "leukemic infiltration" which were present in these cases excluded to our satisfaction the possibility that the hematopoietic change was an unusual response to ordinary infection.

#### MULTIPLE MYELOMA, MYELOID TYPE

Cases 7 and 8 would have been diagnosed multiple myeloma, and it would have been assumed that the tumors were of the plasma cell type had not biopsies been made. It must be admitted that we have no proof that the bone marrow was not diffusely involved in case 7 or even in case 8. It must also be admitted that we have no proof that the whole bone marrow was involved in the patient whose condition was diagnosed diffuse aleukemic myelosis. Indeed, one can see here almost every gradation from ordinary leukemic myelosis to single extramedullary tumors made up of myeloid cells. The subdivisions which we have made are for convenience and not because we are convinced that they are warranted. The criteria for the clinical diagnosis for patients assumed to have localized lesions in the bone marrow differ somewhat from the findings in those in whom a diffuse hyperplasia of the bone marrow seemed more likely. In cases 7 and 8 the blood smears were nearly normal, and secondary hemorrhagic purpura was

not present. Anemia was marked in case 7 but not in case 8. Roentgenograms gave positive evidence of lytic lesions in both. The consumption of oxygen was increased in case 7, but was in the low normal range in case 8. The disease process was considerably more widespread and more active in the former case.

Quantitative determinations of the various constituents of the blood are of considerable diagnostic value in a few of the cases in this group. Plasma proteins may be markedly abnormal, as demonstrated in case 7. Perlzweig, Delrue and Geschickter<sup>11</sup> reported a case of multiple myeloma of the plasma cell type in which the globulin fraction was found to be 11.04 per cent on one occasion. Shirer, Duncan and Haden<sup>12</sup> reported two cases of myeloma in which an apparent increase in globulin was proved to be due to Bence-Jones protein in the plasma. Our case 7 and that of Perlzweig and his associates, as well as one of Shirer's cases, showed Bence-Jones proteinuria. Reimann<sup>13</sup> reported a case of multiple myeloma (plasma cell type) in which the total plasma protein was 10.12 per cent, of which 5.48 per cent was fibrinogen, 2.37 per cent euglobulin, 1.47 per cent pseudoglobulin I and II and 0.9 per cent albumin. The urine did not contain Bence-Jones protein. This patient's serum produced rapid rouleau formation in his own as well as in various donor's corpuscles, so that blood grouping, as well as erythrocyte counting, was impossible. The rapid rouleau formation was attributed by the author to hyperproteinemia. In our case 7 there was no special tendency to rouleau formation, but the Wassermann reaction of the blood was twice anticomplementary.

The blood calcium was repeatedly determined in case 7 with the following findings in milligrams per hundred cubic centimeters: 17.1, 16.7, 16 and 15. Phosphorus was found to be 2.66, 2.8, 3.5 and 3.8 mg. per hundred cubic centimeters. In a patient with carcinomatosis of the bone marrow from carcinoma of the stomach, Dr. C. Van Epps of this hospital found the blood calcium to be 18.5 mg. and the blood phosphorus 4.6 mg. Snapper<sup>14</sup> thinks that hypercalcemia points to hyperparathyroidism only if hypophosphatemia is also present. In cases 5, 6 and 7, the blood calcium and phosphorus values were normal. The urinary calcium in case 7 was much increased, but determinations were

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11. Perlzweig, W. A.; Delrue, G., and Geschickter, C.: Hyperproteinemia Associated with Multiple Myelomas, *J. A. M. A.* **90**:755 (March 10) 1928.

12. Shirer, J. W.; Duncan, W., and Haden, R. L.: Hyperproteinemia Due to Bence-Jones Protein in Myelomatosis, *Arch. Int. Med.* **50**:829 (Dec.) 1932.

13. Reimann, H. A.: Hyperproteinemia as a Cause of Autohemagglutination: Observations in a Case of Myeloma, *J. A. M. A.* **99**:1411 (Oct. 22) 1932.

14. Snapper, I.: Calcium and Inorganic Phosphates of the Serum in Hyperparathyroidism and Myeloma, *Acta brevica neerland.* **1**:25, 1931; abstr., *Nutrition Abstr. & Rev.* **1**:470, 1932.

not made in the other cases. The level of the blood calcium may parallel the destruction of the bone, but we have no proof of this fact. The lesions of the bone may not have been progressing in the patients with normal levels of blood calcium, but this fact could have been better ascertained had we studied the calcium balance. The plasma cholesterol was moderately decreased in cases 7 and 8.

#### EXTRAMEDULLARY MYELOMAS

Cases 9 and 10, though not exhaustively studied, failed to show any of the chemical or cytologic abnormalities which were seen in the other groups.

It is to be regretted that our patients were not all studied completely. Patients such as these present a number of interesting abnormalities, and the changes are most interesting because they are so inconstant. We have expended most of our efforts in an attempt to establish criteria for a clinical diagnosis in these cases, since it is obvious that unless the diagnosis can be made clinically, metabolic studies will be impossible.

In the absence of a leukemic blood picture, the following circumstances should suggest the possibility of a hematopoietic disease of the types under discussion:

1. A severe unexplained anemia with a color index of about 1 and with a moderate increase in reticulocytes.
2. Hemorrhagic purpura which does not respond to transfusions of blood.
3. Tumefaction of the gums.
4. Unexplained enlargement of the spleen or lymph nodes.
5. Symptoms of arthritis without selective atrophy of the muscles, increased tendon reflexes or palpable changes in the joints.
6. Nerve root or deep bony pain.
7. Lytic lesions in bones (for example, lesions of the ribs seen in a roentgenogram of the chest).
8. A leukopenia with a shift to the left in an afebrile patient.
9. Erythroblasts found unexpectedly in a smear.
10. Pathologic fractures.
11. High consumption of oxygen in a patient without fever or exophthalmic goiter.
12. Unexplained acute enlargement of the breasts or ovaries.

Of less moment are the following:

1. Reddish-gray nonliquefied tissue discovered at operation for osteomyelitis.



2. Priapism.
3. Abnormally high plasma globulin or fibrinogen.
4. Unexplained hypercalcemia or hypocholesteremia.
5. Bence-Jones proteinuria.
6. Abnormally rapid rouleau formation (Reimann).
7. Unexplained anticomplementary Wassermann tests.

A complete study of a patient with aleukemic myelosis, either diffuse or localized, would require a considerable amount of laboratory and metabolic work. The same is true of multiple myeloma of the plasma cell type. The confused state of our information concerning these diseases may well be due to the fact that it is incomplete.

#### SUMMARY

Ten cases are reported in which a common feature was myeloid hyperplasia.

Two cases were ordinary instances of leukemic myelosis, except that in the course of each there developed an almost completely aleukemic period. In one case the aleukemic period was thought to be due to irradiation of the spleen; in the other, it was "spontaneous."

Four cases thought to be diffuse hyperplasia of the myeloid tissue were characterized by severe anemia, leukopenia, a few abnormal leukocytes, secondary hemorrhagic purpura, changes in the bones and extramedullary collections of myeloid cells.

Two cases were indistinguishable from ordinary multiple myeloma, except that the tumors were made up of myeloid cells instead of plasma cells. One case presented chemical changes sometimes seen in multiple myeloma of the plasma cell type.

In the last two cases extramedullary myeloid tumors were present without definite evidence of disease of the bone marrow.

NOTE.—Since this manuscript was prepared, a boy, 10 years of age, with features similar to those in case 4 has been studied. The outstanding features were swollen gums, numbness of the chin and an osteolytic lesion of the mandible.

# PERIPHERAL VASCULAR PHENOMENA

## III. THE PERIPHERAL PULSE VOLUME IN OCCLUSIVE ARTERIAL DISEASES

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Early in the study of peripheral pulse volume by means of the plethysmometer described by Johnson,<sup>1</sup> it became evident that in persons suffering from occlusive disease of the arteries of the extremities, the pulse volume wave deviated sharply in size and contour from that obtained in normal persons. This change was found to be remarkably constant and could be repeated day after day, so that it was frequently possible to identify the patient by the appearance of the tracing (fig. 3). These changes were more uniform than were the deviations from the normal in persons with either valvular defect or myocardial impairment.<sup>1</sup>

It will be demonstrated that the character of the wave is not dependent on changes in the peripheral capillary bed, except that as in the normal state<sup>1</sup> and in Raynaud's disease the size of the wave diminishes with capillary and arteriolar vasoconstriction. Immediately after the induction of vasodilation by heat, the wave assumes a size and form which are uniform when the experiment is repeated under similar conditions, and they remain so until there has been an alteration in the occlusive pathologic process or a release of the angiospasm. Excursions of uniform maximum size for the subject and for the digit employed are the result. It is because of this constancy of observations that the method is offered as a diagnostic aid in the study of peripheral vascular disease.

Of the objective methods of study of these defects, it has been said that observations on the skin temperature are the most important. Certainly this method is most widely used both in the diagnosis of disease and in the differentiation between organic occlusion and vascular spasm. It is an indirect method, and the skin temperature is subject to many external variations such as room temperature, humidity and air currents,

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1. Johnson, C. A.: Studies on Peripheral Vascular Phenomena: I. A New Device for the Study of Peripheral Vascular Phenomena in Health and Disease, Surg., Gynec. & Obst. **55**:731 (Dec.) 1932.

2. Footnote 2 has been deleted by the author.

as well as many unknown variables, such as perspiration, heat radiation and fluctuations of the vasomotor system, all intangible and constantly varying in degree, so that the same conditions cannot be repeatedly imposed with certainty.

In addition to determining the condition of the larger vessels by palpation of the pulse in various locations and noting change in color with change in posture and the presence or absence of integrity of tissue, various other methods have been used or suggested. Oscillometric measurements, the histamine tests,<sup>3</sup> direct readings of the blood pressure in various arteries of extremities and the recent experimental observation of Allen and Camp on direct arteriography<sup>4</sup> have real value, but are either indirect or difficult of application.

The method here offered has most of the applications of the method in which the skin temperature is studied. It is a more direct measure of the circulation and can be used in the same manner as observations of the skin temperatures in the differentiation between organic and angiospastic obstruction to circulation. In addition, an objective permanent record is available.

#### METHOD OF STUDY

A simple plan was found to be adequate for the induction of standard conditions which resulted successfully in producing uniform results in each case: The patient is brought into the observation room, the temperature of which remains fairly constant, and is allowed to remain for a few minutes. Tracings of the pulse waves are then taken after observation of the surface temperatures. Tracings of the digits of the upper extremities are taken with the patient sitting comfortably in a chair with both arms resting on a table in such a manner as to secure complete relaxation with the hands at approximately the cardiac level. It is necessary to eliminate as much as possible the annoying element of tremor and somatic muscular movements which otherwise interrupt the smooth continuity of the tracing. The digits of the lower extremities are studied best with the patient in a recumbent position, although some of the records have been taken with the patient in the sitting posture. Tracings are then repeated immediately after the extremities have been immersed in water at 45 C. for ten minutes and rapidly dried. Observations have also been made after the induction of artificial fever by the injection of foreign protein and following ramisectomy and sympathetic ganglionectomy in one case previously reported.<sup>5</sup> The reflex effect of cold has also been determined, especially in Raynaud's disease and in thrombo-angiitis obliterans in which the clinical history has suggested undue vasoconstriction with cold.

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3. de Takáts, G.: Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, *Arch. Int. Med.* **48**:769 (Nov.) 1931.

4. Allen, E. V., and Camp, J. D.: Roentgenography of the Arteries of the Extremities, *Proc. Staff Meet., Mayo Clin.* **7**:46:657 (Nov. 16) 1932.

5. Johnson, C. A.; Scupham, G. W., and Gilbert, N. C.: Studies on Peripheral Vascular Phenomena: II. Observation on Peripheral Circulatory Changes Following Unilateral Cervical Ganglionectomy and Ramisectomy, *Surg., Gynec. & Obst.* **55**:737 (Dec.) 1932.

The following are typical examples of peripheral arterial diseases of various types illustrating the deviation from the normal in the peripheral pulse volume wave in each instance.

#### REPORT OF CASES

##### CASE 1.—*Diabetic arteriosclerosis.*

B. D., aged 62, a Negress, entered St. Luke's Hospital in coma with severe diabetes. There was moderate sclerosis of the radial and brachial arteries but no impairment of circulation in the upper extremities. The left leg had been amputated previously because of diabetic gangrene. Circulatory impairment existed in the right foot; the dorsalis pedis and posterior tibial pulsations were not palpable; loss

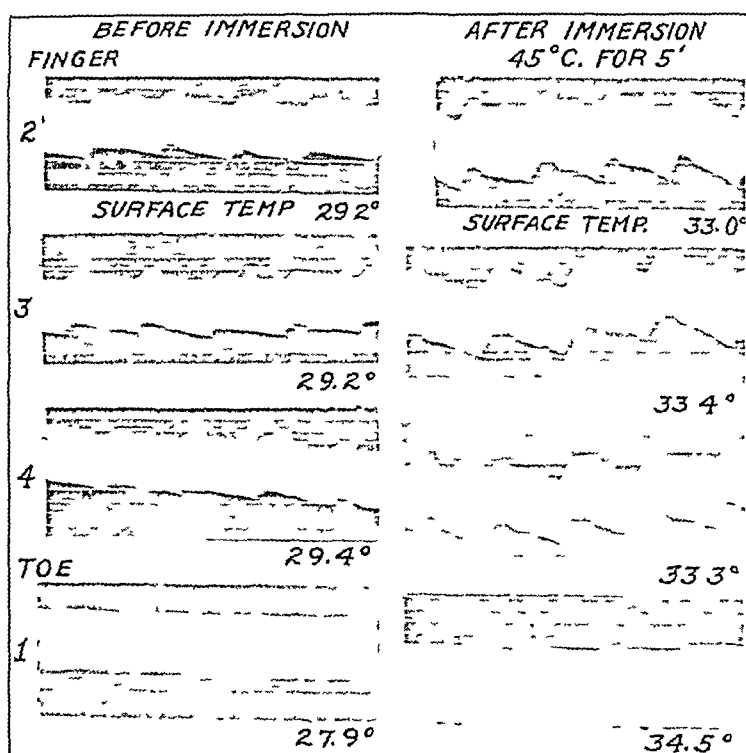


Fig. 1.—Tracings made from a patient with diabetic arteriosclerosis in whom gangrene developed four months later. The tracings are shown from the second, third and fourth fingers of the right hand with a normal response in these fingers before and after immersion in water at 45 C. for five minutes. In finger 3 the pulse volume is approximately 0.01 cc. before immersion, and 0.02 cc. following vasodilation of heat, showing a normal response in spite of an obvious arteriosclerosis. The lowest tracing shows the pulse volume of the right first toe with a very faint increase in volume before, and no significant change following, immersion. There were no subjective symptoms, although the other foot had been previously amputated for gangrene. The significance is evident. The space between the horizontal lines indicates 0.01 cc.

of heat was marked, and the foot was always cold. The surface temperature of the first toe averaged 27.9 C.

The tracing of the peripheral pulse volume (fig. 1) shows normal size of the wave in the right hand at room temperature with an average change in volume in the second finger of approximately 0.01 cc. After immersion in water at 45 C. for five minutes, this was increased to 0.02 cc. Similar changes occurred in all the

digits in the upper extremity. This constitutes a normal response and shows no impairment in circulation in spite of an obvious arteriosclerosis.

It will be noted that the pulse volume wave from the right foot is faint at room temperature and shows practically no change after induction of the vasodilation of heat. Subsequently, about four months later, gangrene developed in this foot, and amputation was necessary. Peripheral vasodilation failed to increase the size of the wave because obstruction in the larger arteries so limited the blood flow that the volume could not be increased in the capillary and arteriolar bed even with dilation. This demonstrates the findings of a severe degree of occlusion.

CASE 2.—*Senile arteriosclerosis with occlusion.*

J. S., aged 62, a white man, entered St. Luke's Hospital in the surgery A service of Dr. H. E. Jones. He had been having pain in the left foot for the past three years with some discoloration, and more recently, ulceration. He had had a previous infection of the toe of the same foot about five years before, but it had entirely healed. The pain was described as sharp and shooting, of from five to ten minutes' duration. This gradually became worse so that he had to use a cane. Then he began to have pain at rest, but change in the position of the foot gave some relief. Both feet were so susceptible to cold that it was difficult to keep them warm. The left foot became more discolored and painful. About three months before admission an ulcer appeared on the inner surface of the foot above the heel. This healed, but later opened again; since then the ulcer had increased in size.

The patient was a truck driver and had been a heavy smoker and drinker. He said that he had never had syphilis and that except for the complaints on entrance he had always been well.

Physical examination revealed moderate sclerosis and beading in all peripheral arteries, which were tortuous. The blood pressure was 140 systolic and 84 diastolic. The heart was normal except that there were frequent extrasystoles. The left foot had an ulcer on the medial aspect below the malleolus about 5 cm. in diameter with slightly raised edges of granulation tissue. There were two smaller ones above and anterior within 1.5 cm. of the larger one. Both feet were cold and showed dusky discoloration when dependent, with marked change to pallor when elevated. The dorsalis pedis and posterior tibial arteries could not be palpated in either foot. The femoral and popliteal pulsations were good. The veins seemed to be normal with no varicosities. The Kahn test was negative; renal function was unimpaired, and the blood showed no anemia. Observations on the skin temperature showed the hands to be warm, averaging about 34 C., with marked loss of heat in both feet; the temperature of the right first toe averaged 28.5 C., and that of the left, 27 C. The peripheral pulse waves in both hands were equal, and the right is shown in figure 2. It will be noted that there was a normal response at room temperature averaging 0.011 cc., with an increase to 0.022 cc. following immersion of the hand in water at 45 C. for ten minutes. Tracings of the first toe on both feet show no perceptible pulsation either before or after immersion in hot water. This would indicate a high degree of occlusion of the arteries of the feet and legs.

CASE 3.—*Thrombo-angiitis obliterans.*

P. C., aged 37, a white man, entered St. Luke's Hospital in the orthopedic service of Dr. Ryerson, complaining of pain in the right foot and leg. The first evidence of circulatory disturbance was three years before admission when he had pain in the left second finger. A small ulcer appeared, which finally healed. The finger became smaller at the end. While at work at the stockyards his duties took him to a cold storage room frequently. He noticed that ten minutes in the cold

room resulted in the right second finger turning white. There was no abrupt change to red afterward, but a return to normal color slowly. The pain stopped when he came back to a warm room. The ends of several fingers were successively involved. His feet began to trouble him about nine months before admis-

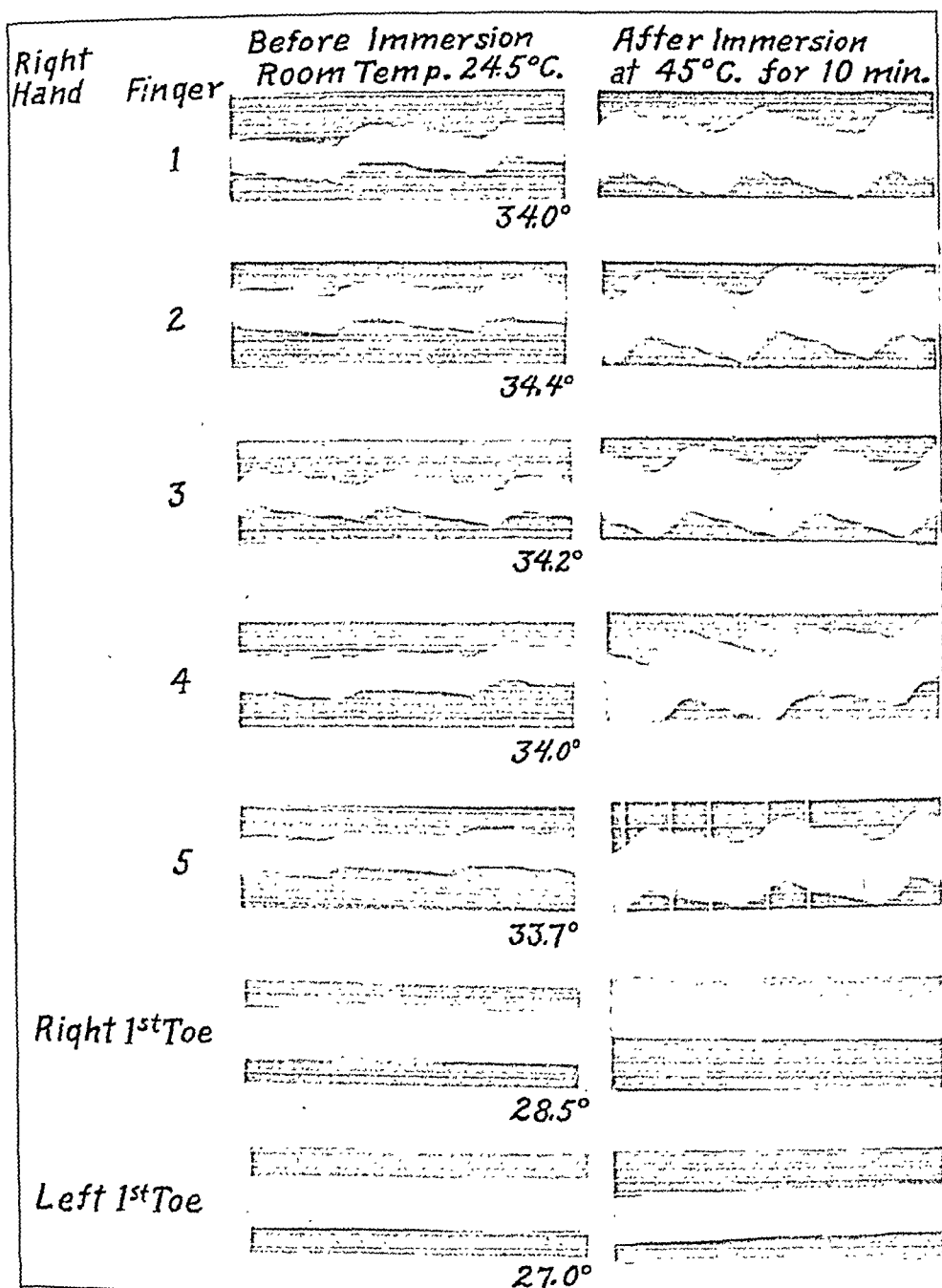


Fig. 2.—Tracings from a patient with senile arteriosclerosis with an ulcer on the left foot. There were no subjective symptoms in the right foot. The tracing of the peripheral pulse volume of the fingers of the right hand indicate unobstructed vessels. Tracings from the first toe of both feet show no pulse wave before, and no significant change following, vasodilation, indicating high grade occlusion. The skin temperatures are low.

sion. He would have pain in the region of the arch below the ankles if he walked about four blocks. He would then sit down and rest following which he could

walk again. Pain while resting began in the foot two or three weeks before admission. Since then he had been unable to stay in bed at night because of pain. His hands no longer caused any complaint.

He was a heavy smoker and drinker and smoked about from twenty to thirty handmade cigarets a day.

Examination showed a well developed, healthy appearing adult whose only pathologic findings were referable to the arteries of the hands and feet. There was apparent loss of heat in the right foot, which showed dependent rubor, and pallor on elevation. There was a gangrenous ulcer of the first toe. Most of the first phalanx was gone, and the bone was exposed. It was very tender and constantly painful. There were moderate swelling and redness and some evident secondary infection.

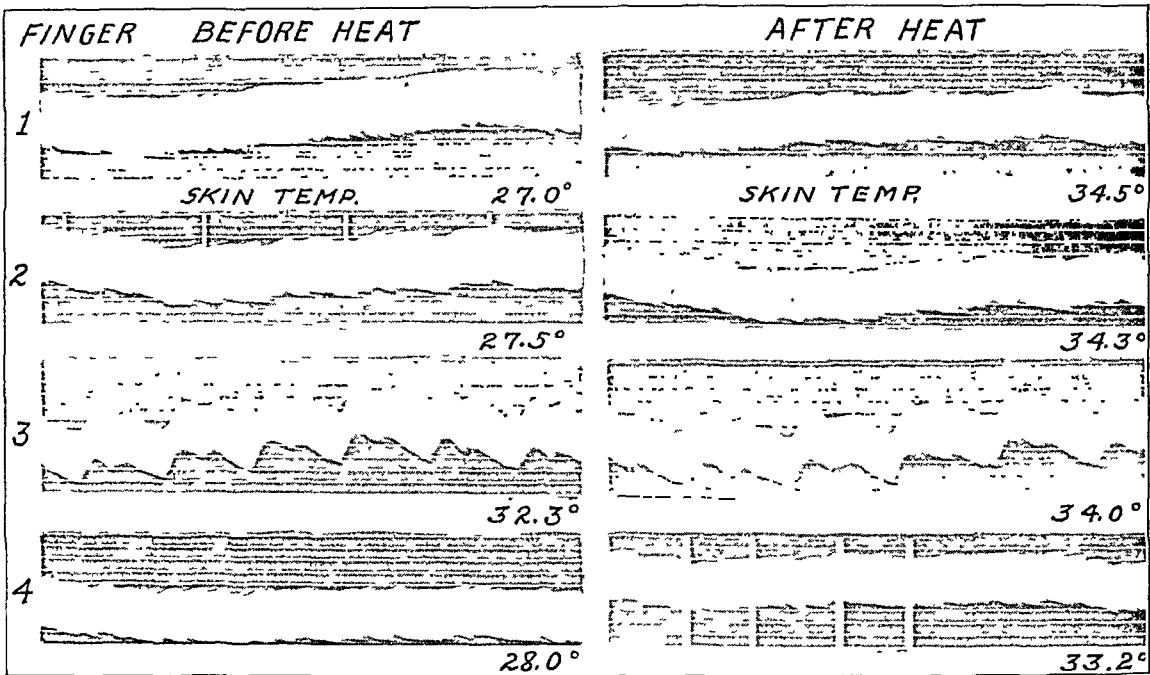


Fig. 3.—Tracings of a patient with thrombo-angiitis obliterans. The tracing of the right hand shows the pulse waves in fingers 1, 2, 3 and 4. There was past history of circulatory disturbance, but none at the time of the tracing. Fingers 1, 2 and 4 show definite evidence of occlusion with only a faint pulse wave before and after vasodilation by heat; no increase is noted. The irregular and frequent waves are due to tremor and somatic movement. Finger 3 shows a large pulse wave and a high skin temperature at room temperature and no appreciable increase following the vasodilation of heat, indicating a persistent vasodilation, a constant feature always noted in this case.

The dorsalis pedis and posterior tibial arteries were not palpable; the popliteal and femoral pulsations were normal. The left dorsalis pedis and posterior tibial arteries were palpable. The right radial artery was not palpable, but the ulnar was intact; the brachial artery seemed normal. The fingers of the right hand, except the third, were cold. The larger vessels in the left hand and arm were unimpaired.

The Wassermann reaction was negative. Renal function was normal. The blood showed no anemia, and viscosity was normal.

The peripheral pulse volume could not be determined in the right foot because of gangrene of the toe. In the left, it was unimpaired. The most interesting findings were demonstrable in the right hand (fig. 3). There were no perceptible pulse waves at room temperature except in the third finger in which the wave was maximum. The skin temperatures, it will be noted, were low in the first, second and fourth fingers, and in the third finger were nearly five degrees higher. After immersion of the hand in hot water at 45 C. for ten minutes, there was no essential change. A faint pulsation was noted in the first and second fingers, but this is questionable because of the small oscillations due to somatic tremor. In the third finger with a large pulse volume there was no increase in volume following vasodilation by heat, showing that the dilation of the capillaries and arterioles was complete and apparently fixed. This was a constant finding in this patient, and a similar condition has been noted in another case of thrombo-angiitis obliterans. It is apparent that a persistent local vasodilation may occur in thrombo-angiitis obliterans and may account for the subjective sensations of heat and burning that are occasionally encountered in this disease, causing confusion with erythromelalgia, which has been noted.<sup>6</sup>

#### COMMENT

The pulse volume of a digit is shown by the height of the pulse wave in the tracing. It represents the increased amount of blood in the capillaries and the arterioles of the digit examined, resulting from systole of the left ventricle of the heart.<sup>1</sup> Conditions which modify the progress of blood through the arteries to the digit will conceivably modify the size of the wave, provided the heart is competent and has normal mechanism, and the pulse pressure is fairly well maintained. In the cases presented these factors were unimpaired.

The effects of external temperature and other stimuli on the capillaries and arterioles cause so much fluctuation in vasoconstriction and dilation by both direct and reflex action that full consideration of obstruction above the arteriolar level cannot be given to the findings unless there is certainty that the capillaries and arterioles are dilated and capable of responding to an uninterrupted blood flow. This is accomplished by immersion of the extremity in water at 45 C. for ten minutes, a procedure which eliminates the uncertainty of vasomotor activity for the period of observation.

If occlusion exists above the arteriolar level, the amount of blood delivered to the digit is diminished, and the size of the pulse wave varies with the degree of stenosis regardless of its location in the artery. The method as here described gives no indication of the location of the occluding process unless it can be demonstrated that the arteries at a certain level above are intact; then it may be assumed that the site is between that point and the digit examined. The presence

6. Brown, G. E.: Erythromelalgia and Other Disturbances in the Extremities Accompanied by Vasodilatation and Burning, *Am. J. M. Sc.* **183**:468 (April) 1932.



of an established collateral circulation does modify the findings. If it is entirely adequate, a normal response might be expected.

Angiospastic phenomena may be differentiated in this manner if the vasodilator stimulus of heat applied externally is of sufficient intensity. That this occurs is questionable in the case of spasm in larger vessels, such as the angiospasm occurring in Buerger's disease. That it occurs in the vasospastic phenomena of the smaller vessels is shown by the

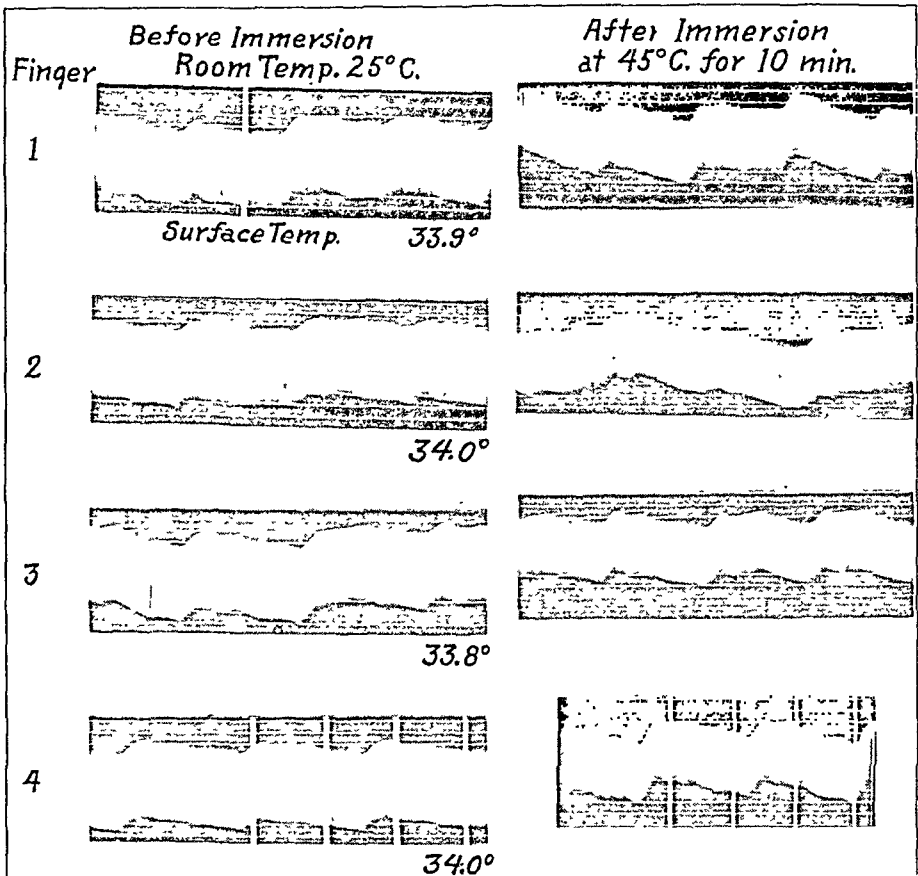


Fig. 4.—Tracings of four fingers of the right hand of a patient with thromboangiitis obliterans. No subjective symptoms were noted in the hands. Both legs were previously amputated. Normal pulse waves at room temperature with a normal response to heat are shown in fingers 1 and 4, but in 2 and 3 there is no increase in pulse wave. This is interpreted as evidence of a mild grade of impairment in the blood supply of these fingers.

fact that in Raynaud's disease the response to heat is a normal vasodilation, but with the stimulation by the proper degree of cold a prolonged vasoconstriction results, with a marked delay of the normal reactive peripheral vasodilation of the smallest vessels. Lower temperatures may result in a reactive vasodilation. These phenomena are discussed in a later communication.

That other stimuli do result in the release of spasm in the arteries may be demonstrated by figures 4 and 5, which represent the results of artificial fever in a case of thrombo-angiitis obliterans without marked involvement of the hands and without subjective symptoms referable to them. It will be noted that at room temperature there was a nearly normal pulse wave in the fingers of the left hand. Following the vasodilation of heat, there was a normal increase of pulse volume in fingers 1 and 4, but in fingers 2 and 3 there was no increase. The

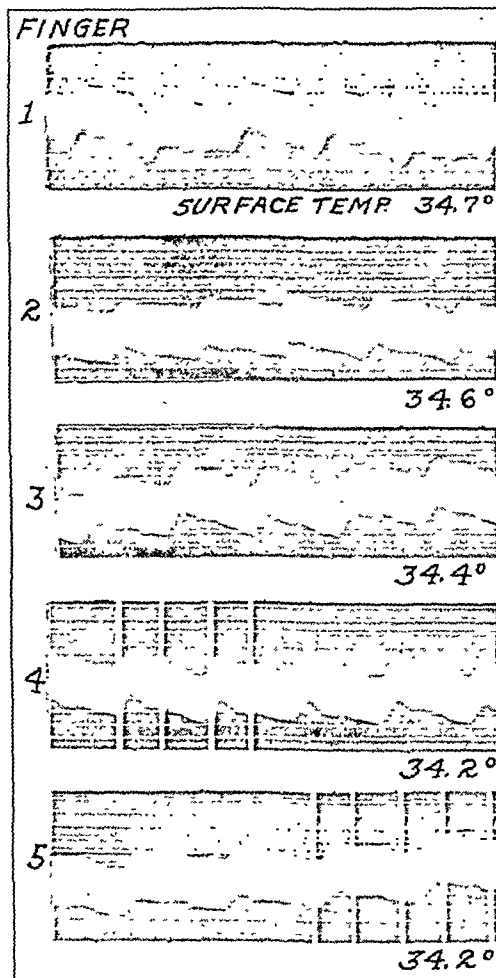


Fig. 5.—Same as figure 4 but following the artificial induction of fever without a significant fall in blood pressure. A small increase in pulse volume can be noted in finger 2 and very definite increase in finger 3, indicating the release of spasm not accomplished by immersion in hot water.

pulse waves were of about the same size, namely, about 0.008 cc. in both fingers before and after heat. This would indicate impairment of the circulation to these fingers, which probably existed in the smaller arteries of the digits themselves as the radial and ulnar arteries were intact. Following the induction of fever by intravenous injection of typhoid vaccine at an oral temperature of 101 F. (fig. 5), there was a definite increase of the pulse volume to 0.012 cc. in finger 2 and to

0.02 cc. in finger 3, indicating the release of spasm during fever. This interpretation is believed to be correct only if the pulse pressure is maintained and the heart is competent.<sup>5</sup> Other work, to be reported later, has led to the belief that an increase in peripheral pulse volume does not always occur with the artificial induction of fever, but may actually be diminished because of a coincident fall in blood pressure, or because of myocardial impairment with a fall in pulse pressure.

It may be noted here that in this patient, who had thrombo-angiitis obliterans of severe type which had resulted in the amputation of both legs several years previously, it was possible to demonstrate impairment of the efficiency of the circulation in the hands, although as yet there were no subjective symptoms and no demonstrable alterations in the skin temperature. It has been possible to demonstrate disease of the vessels in extremities other than the ones complained of in several instances, and it is believed in an early stage before the pathologic process had advanced to the degree from which there was ischemia sufficient to produce symptoms. This applies to thrombo-angiitis obliterans as well as to arteriosclerosis, and is particularly valuable in the determination of vascular efficiency in diabetes. Attention must be called to the fact that in size and contour the peripheral pulse wave in the lower extremities<sup>1</sup> differs from that noted in the upper, especially when tracings are taken with the patient in the sitting position. The wave is smaller and more sharply peaked.<sup>1</sup>

Observations on the differentiation of peripheral arterial spasm and occlusion by the nerve block method of Scott and Morton<sup>7</sup> and by the diagnostic blocking of sympathetic nerves<sup>8</sup> have been made. The method is applicable, as a marked temporary increase in pulse volume has been recorded immediately following sympathetic ganglionectomy, as reported in a previous paper.<sup>5</sup> The results with peripheral nerve block will be reported later.

Further observations on the effect of heat and cold stimuli on the capillaries and arterioles is in progress, but the essential observations necessary for the evaluation of the method in occlusive arterial diseases have been given.

#### SUMMARY

1. A method of study of the peripheral circulation has been applied to the diagnosis of peripheral vascular diseases.

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7. Scott, W. J. M., and Morton, J. J.: The Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, *J. A. M. A.* **97**:1212 (Oct. 24) 1931.

8. White, J. C.: Diagnostic Blocking of the Sympathetic Nerves to the Extremities with Procaine, *J. A. M. A.* **94**:1382 (May 3) 1930.

2. It is an objective method, more direct and in some respects more reliable than the determination of skin temperature. The procedure is simple and easy of application, and with it permanent records may be obtained for accurate subsequent comparison.

3. It is believed to be applicable, as a criterion, to all the methods for differential diagnosis between organic occlusion and angiospasm, in the same manner that determinations of skin temperature are now used.

4. It is valuable in the determination of occlusion in the smaller arteries of a digit when other methods are not applicable.

5. Mild degrees of partial occlusion in early cases in which skin temperatures show no reliable variation and in which subjective symptoms are confusing can be determined.

6. The method is simple and easy of application and interpretation.

# LOBAR ATELECTASIS AS A CAUSE OF TRIANGULAR ROENTGEN SHADOWS IN BRONCHIECTASIS

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AND

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A few years ago we became interested in the occurrence of triangular basal shadows in roentgenograms of the chest of patients suffering from bronchiectasis. The first patient showing a triangular basal shadow discovered by one of us (W. P. W.) afforded an excellent opportunity for the investigation of the production of this type of shadow, as it was possible to study roentgenograms of the chest before and after the injection of iodized poppy seed oil 40 per cent into the bronchi, and later to remove the part of the lung causing the shadow and to observe its gross and microscopic appearance.

The shadows are seen as homogeneous areas of increased density, triangular in shape, with one side of the triangle along the mediastinum, the lower side parallel with the diaphragm and the hypotenuse running from near the root of the lung to join the lower side at varying distances from the mediastinum. If the shadow occurs on the left side, as in figure 1 *A*, it usually lies behind the cardiac shadow which, with the remaining structures in the mediastinum, is pulled toward the affected side. If the shadow occurs on the right side, the mediastinum is pulled toward the right. The diaphragm on the affected side is usually high.

Before discussing the results of our investigation regarding the significance and cause of the shadows, a brief review of the literature on the subject will be given. In 1925, Armand-Delille, Lévy and Marie,<sup>1</sup> in a paper on the use of iodized oil in the diagnosis of bronchiectasis in children, referred to the presence of triangular basal shadows in two of three cases, but did not comment on their significance. The same year, Comby,<sup>2</sup> in a discussion following a paper by Guinon and Levesque, stated that these roentgen shadows in children often

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1. Armand-Delille, Lévy and Marie: *Rev. franç. de pédiat.* **1**:125, 1925.

2. Comby, J., in discussion on Guinon, L., and Levesque, J.: *Sur les adénopathies trachéo-bronchiques non tuberculeuses; examen radiologique*, *Bull. Soc. de pédiat. de Paris* **23**:151, 1925.

indicated bronchiectasis. In a roentgen study of bronchiectasis published in 1926, Singer and Graham<sup>3</sup> called attention to the triangular shadow densities in many cases of bronchiectasis, and stated:

In the cases that have been operated upon, these triangular shadows have been found to represent atelectatic bronchiectatic lower lobes with the characteristic cyanotic appearance and indurated feeling on palpation. We have been surprised when the chest cavity was opened to find that the unaffected lobe or lobes had hypertrophied so much as to fill out the chest cavity and surround the collapsed lobe. In the roentgen plate these collapsed lobes manifest themselves as dense shadows in the region of the cardio-diaphragmatic region.

Injections of iodized oil were not used. In 1927, Rist, Jacob and Trocmé<sup>4</sup> investigated seven patients in whom roentgen films of the

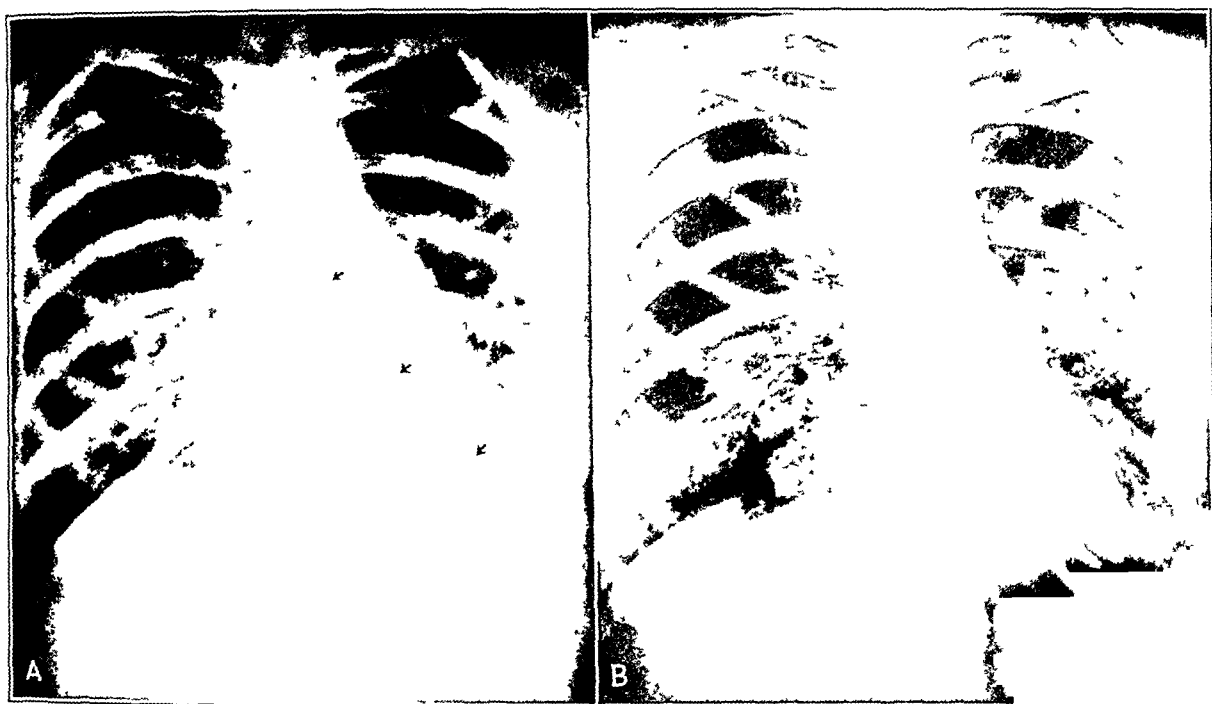


Fig. 1 (case 1).—*A*, a triangular shadow occurring on the left side, behind the shadow of the heart, which, with the remaining structures of the mediastinum, is pulled toward the affected side. *B*, appearance following the injection of iodized oil. The bronchi in the left lower lobe show cylindric dilatation.

chest showed triangular basal shadows. Previously these shadows were considered to be diagnostic of mediastinal pleurisy, but by injection of iodized oil, Rist and his co-workers were able to demonstrate the presence of bronchiectasis within the area of the triangular basal shadow. They came to the conclusion that the occurrence of these shadows was due in part to pleural thickening and in part to changes within the lung, both conditions developing secondarily to a primary bronchiectasis. Later in the same year these observations were con-

3. Singer and Graham: *J. Missouri M. A.* **19**:390, 1922.

4. Rist, Jacob and Trocmé: *Ann. de méd.* **21**:144, 1927.

firmed by Sergent and Bordet.<sup>5</sup> Wallgren,<sup>6</sup> in 1928, reported five cases of triangular basal shadows occurring in children and discussed their diagnostic significance. In the first case a right basal shadow disappeared after the removal of 20 cc. of fluid from the pleural cavity, and the shadow was considered to have been caused by a pleural effusion. Compression of the bronchus to the middle lobe by an enlarged gland produced atelectasis and caused the shadow in the second case. After two and one-half months the gland became smaller, the obstruction was removed, and the result was the re-aeration of the lobe and the disappearance of the shadow. The other three were cases of bronchiectasis in which there were histories of cough and expectoration of many years' duration. Wallgren noted that the heart was displaced to the side of the triangular shadow in the case of bronchiectasis, whereas in the case of pleural effusion it was displaced to the healthy side. In two cases he was able to show that the bronchiectasis was present for five years before the development of the triangular basal shadow. He considered that the changes within the lung, and not the thickening of the pleura, were the cause of the shadow.

In our study of bronchiectasis, particularly in reference to triangular basal shadows, we have endeavored to determine the significance and cause of the shadows, and have produced them experimentally. We believe that the work presented shows definitely the mechanism of their production and by so doing sheds considerable light on the problem of the cause of bronchiectasis. With the use of iodized oil injected into the bronchial tree, we were able to demonstrate that invariably these triangular shadows contain dilated bronchi. The bronchiectasis is usually cylindric (fig. 1 *B*), but occasionally saccular dilatations are present. The bronchi appear closely placed, with very little tissue between them, as compared with normal bronchi. That the triangular shadows contain bronchiectatic dilatations was also proved by bronchoscopic visualization and by examination of the surgically removed diseased area (lobectomy). We therefore feel that in any case in which a triangular shadow is present in a plain roentgen film of the chest, a tentative diagnosis of bronchiectasis is justifiable, and that the injection of iodized oil is indicated to confirm the diagnosis.

Not only have these triangular shadows invariably indicated the presence of bronchiectasis, but they have occurred frequently in the cases which we have studied. About 6 per cent of all our proved cases of bronchiectasis have shown them. They are therefore of definite diagnostic value, particularly in view of our difficulty in otherwise diag-

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5. Sergent and Bordet: *Bull. et mém. Soc. méd. d. hôp. de Paris* **51**:742, 1927.

6. Wallgren: *Beitr. z. Klin. d. Tuberk.* **69**:641, 1928.

nosing cases of bronchiectasis roentgenologically without the injection of iodized oil. This fact, along with the frequent occurrence of the shadows, makes them not a roentgen curiosity but a definite diagnostic aid. They have not received the attention which we believe their diagnostic value warrants.

Having become fully convinced of the diagnostic importance of the shadows, our next concern was the manner of their development. Obviously they were not due to dilated bronchi alone, as they were present in only 6 per cent of our cases. The injection of iodized oil into the bronchial tree gave the first indication of the nature of the shadows. By means of these injections the bronchi of the various lobes could be identified and a conception of the position and the size of the lobes obtained. It was found that if the triangular shadow was present on the left side, it invariably represented the left lower lobe. If it occurred on the right side, it represented either the right lower or the right lower and middle lobes. The lobes causing the shadow were much smaller than normal lobes. They had apparently left their normal position in the thorax, becoming greatly reduced in size and appearing as a uniform, dense shadow adjacent to the mediastinum. The upper lobes had enlarged and rotated so as to fill the space in the thorax normally occupied by the lower lobes. This is seen in figure 1 *B*, in which the main bronchus to the left lower lobe is seen to enter the triangular shadow and in which the branches are found only within the shadow. The bronchus to the left upper lobes is seen to supply the lung, occupying all the left side of the thorax except the triangular shadow. In stereoroentgenograms, branches of the bronchus of the upper lobe are seen in areas normally supplied by bronchi of the lower lobe. The lower lobe has therefore left the thoracic wall and a large portion of the diaphragm with which it is normally in contact and is now present as a small dense shadow behind the heart and close to the mediastinum. The remainder of the space which it normally occupied is filled with the expanded and rotated lobes. This conclusion was substantiated by bronchoscopic examination and later by direct observation on opening the thorax surgically in order to remove the bronchiectatic lobe. Similarly, if the shadow is situated on the right side, it could be shown to represent either the right lower lobe or the right middle and lower lobes, greatly reduced in size. In right-sided triangular shadows, therefore, the upper and middle lobes or the upper lobe alone expanded to fill the thorax.

The next problem was to determine the cause of the decrease in the size of the affected lobes. In this connection we were fortunate in being able to observe a case of bronchiectasis of recent origin (about four months) with disease in the left lower lobe. This lower lobe was represented by a triangular shadow (fig. 1 *A*) and was removed by



open operation through the wall of the chest. A brief summary of the clinical findings and the investigation of the case follows:

CASE 1.—Mrs. V. W., aged 23, was admitted to the medical service of the Toronto General Hospital on Feb. 17, 1930. She stated that she was perfectly well until three and one-half months before admission, at which time a dry cough with practically no expectoration developed. Two weeks later she acquired a severe cold in the head; the cough increased, and she began to expectorate about 2 ounces a day of a greenish material. One and one-half months before admission a sharp, severe pain developed in the left side of the chest anteriorly, just below and to the outer side of the heart. She felt quite ill at this time but was in bed only three days. However, she continued to lose weight and to feel ill, and the cough and the expectoration persisted. During the three and one-half months of her illness she lost 25 pounds (11.3 Kg.). She did not feel well for the first two months of her illness. At the time of admission she felt well, her only complaint being cough with about an ounce of greenish-yellow sputum which at no time had a foul odor.

*Examination.*—The patient did not look ill, and there was no clubbing of the fingers. The left side of chest moved less than the right. At the back on the left side a triangular area of dulness could be made out on percussion. Over this area were bronchial breath sounds, crackling medium râles and whispered bronchophony. Repeated examinations of the sputum for tubercle bacilli gave negative results. Roentgen examination (fig. 1 *A*) showed a normal right lung and left apex with a triangular basal shadow behind the shadow of the heart. A tentative diagnosis of a bronchiectatic left lower lobe was made. Local pleural or mediastinal effusion was ruled out by aspiration.

Iodized oil was then injected by the supraglottic route into the left side, and it was seen (fig. 1 *B*) that the main bronchus to the left lower lobe went to the triangular shadow, and that the bronchi in it showed cylindric dilatations. The bronchi appeared quite close together, and one was able to state from the picture after the injection of the iodized oil that the triangular shadow represented the complete left lower lobe, which was about the size of the clenched fist. The left upper lobe had become enlarged and rotated so as to fill the space normally occupied by the lower lobe. This could definitely be determined by making injections into the bronchus to the left upper lobe. The bronchi of the upper lobe were seen in areas normally occupied by the lower lobe. The bronchi in this lobe were normal except for a small strip at the lower edge parallel to the lower lobe, which showed cylindric dilatation.

The final diagnosis of an atelectatic, bronchiectatic left lower lobe was made. A small strip of bronchiectasis was thought to be present at the edge of the left upper lobe. Pneumectomy was considered advisable, and, after a preliminary phrenectomy, the left side of the thorax was opened by Dr. Norman Shenstone and Dr. Robert Janes. No pleural adhesions were found. The left lower lobe was completely collapsed; it had no thickened pleura and did not appear at all like a fibrosed lobe but like an atelectatic one. There was an area along the lower edge of the upper lobe which also looked atelectatic. The left lower lobe, as well as the collapsed portion of the upper lobe, was removed.

The pathologic report of the surgical specimen was made by Dr. W. L. Robinson of the department of pathology.

The gross specimen consisted of a wedge-shaped, soft, rubbery lobe of pulmonary tissue measuring 14 by 9.5 by 2 cm. The bronchi were thick-walled and

dilated to within 2 mm. of the pleural surfaces. Sections of the upper lobe revealed similarly thickened bronchi which presented, however, less dilatation.

Microscopically, sections of the bronchi showed that many of the lumens were almost completely filled with fibrinopurulent exudate. Polymorphonuclears were seen throughout between the lining cells of the mucosa. The epithelial lining was for the most part heaped up and redundant in appearance. Occasional small areas of ulceration were noted. Immediately beneath the epithelium was a fairly broad zone of lymphocytic and plasma cell infiltration in which numerous small congested capillary vessels were seen. A few eosinophils were noted. The peripheral portions of the bronchi showed a well established fibrosis. The cartilaginous plates were embedded in an unusually dense fibrous tissue and showed slight degenerative changes and irregularity in the cellular arrangement. The adjacent pulmonary parenchyma showed a definite collapse, the alveoli of which were lined with a continuous layer of cuboidal epithelium. Elsewhere in a few areas there was fibrosis of the pulmonary parenchyma, in which irregular outlines of alveoli were noticed. The bronchial arteries of the specimen were all thick-walled. Sections of the upper lobe showed a similar picture. It should be noted that the cilia of the mucosal epithelium of the bronchi could easily be identified in the hematoxylin-eosin section. Sections stained for bacteria and for spirochetes were negative.

It is obvious that in this case the bronchiectatic left lower lobe was small and produced a triangular shadow in a roentgenogram because it was atelectatic. There was no pleural thickening and practically no fibrosis of the parenchyma. The triangular shadow in this case was due to an atelectatic or collapsed lower lobe, the bronchi of which were bronchiectatic. It could be seen at operation that the greater part of the space normally occupied by the lower lobe was filled by the expanded upper lobe.

The cause of this atelectasis of the lower lobe was at first obscure. It could not have been due to plugging of the bronchi by secretion, because from the time the patient first came under observation until operation the atelectatic bronchiectatic lobe gave all the physical findings of consolidation with patent bronchi, and the bronchi could be filled by iodized oil. The bronchi appeared patent also at operation, and showed very little secretion. From these findings it was obvious that the atelectasis was probably due to distal obstruction of the bronchi. Careful search was made of the microscopic sections of the lung, and it was seen (figs. 2 and 3) that the terminal bronchioles were closed or practically closed by inflammatory swelling of the bronchial wall. We therefore had the probable cause of the atelectasis of the bronchiectatic lobe.

Besides this direct proof that atelectasis may cause the small lobe producing the triangular shadow, we observed a shadow that appeared and changed in size so rapidly that atelectasis seemed the only possible explanation. A brief outline of the history of the patient in whom this was observed is as follows:

CASE 2.—Miss M. C. S., aged 30, was first seen by us when she was admitted to the Toronto General Hospital on July 3, 1931, almost three months after the



Fig. 2 (case 1).—Microscopic section of the lung.

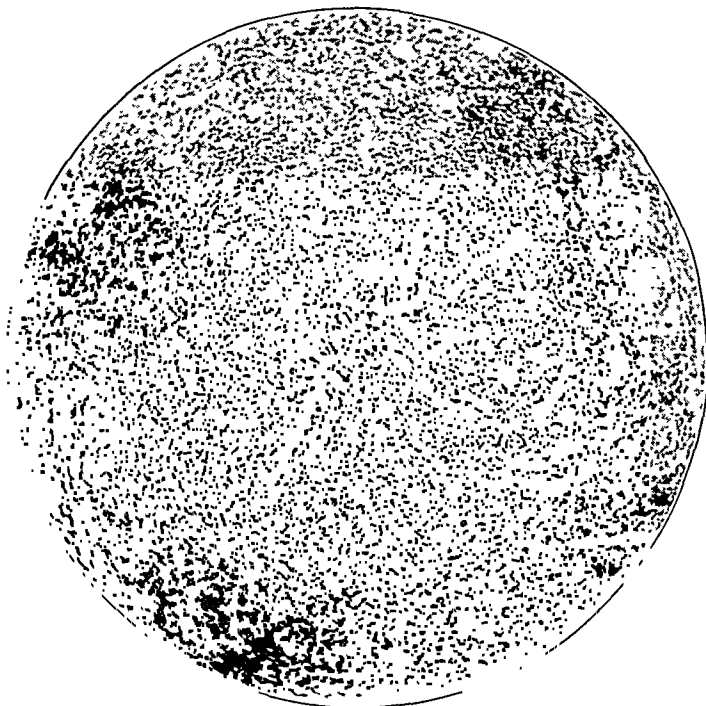


Fig. 3 (case 1).—Another microscopic section, showing the same features as figure 2.

onset of her illness. She gave a long history of cough with slight sputum. This began when she was a child and continued until 1926, when she was 25 years of age. During this time she had considerable nasal and postnasal discharge. In 1926, she had a tonsillectomy, and a bilateral intranasal antral operation was performed. Following these procedures, the cough and the sputum entirely disappeared, and she had no symptoms for five years. At the end of this time, in April, 1931, she had a sudden, sharp pain on the left side of the chest and became quite ill with what was thought to be bronchopneumonia and fibrinous pleurisy on that side. She had a prolonged illness with continual cough and purulent expectoration, and physical findings persisting at the base of the left lung. A diagnosis of bronchiectasis was made by her physician.

Physical examination at this time showed a patient not in good health. She had a slight cough with about 2 ounces a day of purulent sputum which was not foul. The left side of the thorax was restricted in movement, and at the base of the left lung posteriorly there were medium crackling râles. Over this area breath sounds were harsh and bronchovesicular, and whispered voice slightly increased. The right lung showed no abnormal findings. The sputum was repeatedly negative for tubercle bacilli.

Stereoscopic roentgen films of the chest showed heavy bronchial markings at the base of the left lung; the mediastinum was in the midline. The right lung as well as both apexes appeared clear. Iodized oil was injected into the base of the left lung by the supraglottic route, and the roentgenogram (fig. 4A) showed cylindric bronchiectatic dilatation at the base of the left lung. Some of the iodized oil entered the base of the right lung where the bronchi appeared to be normal. A subsequent injection of iodized oil into the right lung revealed no evidence of bronchiectasis. These examinations were made on July 10 and July 12.

The diagnosis of left-sided bronchiectasis was thus confirmed, and the patient was sent back to her home for a month of further convalescence before returning for a left lower lobectomy.

She returned for the operation on August 14. Physical examination at this time gave results identical with those obtained in July. There were no abnormal physical findings in the right side of the chest; the mediastinum was in the midline. On August 17, Shenstone and Janes performed a partial pneumectomy (lobectomy of the left lower lobe). This was preceded by a preliminary phrenectomy. Following the removal of the left lower lobe, a complicating effusion developed on the left side. The effusion was never extensive, and continuous suction drainage of the left pleural space was kept up.

On August 22, it was noted that there was impaired resonance at the base of the right lung, with medium râles and rhonchi. On August 25, eight days after operation, impaired resonance, bronchial breath sounds and crackling râles were found posteriorly on the right side. At this time a portable roentgenogram was taken of the chest, which showed a triangular shadow at the base of the right lung. Instead of finding the mediastinum shifted to the side on which the operation occurred (the left in this case), as is usual following lobectomy, it was shifted to the right side. On September 5, the patient was doing fairly well except that she was coughing up about 3 ounces of purulent sputum a day. On examining the right side of the chest posteriorly, a definite triangular area of impaired resonance, bronchial breath sounds, crackling râles and bronchophony were made out. The triangular area was along the vertebral column, reaching farthest from it at the level of the diaphragm. The mediastinum was shifted to the right side. A roentgenogram (fig. 4B) taken on September 5 showed a distinct triangular basal shadow on the right side corresponding in position to the area over which the



Fig. 4 (case 2).—*A*, a stereoscopic roentgen film showing cylindric bronchiectatic dilatation at the base of the left lung. *B* shows a distinct, triangular basal shadow on the right side corresponding in position to the area over which impaired resonance, bronchial breath sounds, crackling râles and bronchophony were noted. The mediastinum was shifted definitely to the right at this time (Sept. 5, 1931). *C*, a roentgenogram taken after a supraglottic injection of iodized oil. In the triangular basal shadow the bronchi are seen to be close together and to show cylindric dilations. *D*, a roentgen film taken on Oct. 17, 1931, showing a much larger and less distinct triangular arc. The mediastinum has definitely moved back toward the midline.

aforementioned physical findings were elicited. The mediastinum was shifted definitely to the right. On September 19, the patient was still expectorating 3 ounces of purulent sputum a day. Physical signs over the lower part of the right side of chest were not so marked as on September 5. Roentgenograms still showed the triangular shadow plainly but slightly increased in size and not so homogeneous. On October 5, a roentgenogram showed the triangular shadow definitely larger than did the previous film. It was decided to inject iodized oil into this basal shadow. This was done by the supraglottic route, and figure 4 C shows a roentgenogram taken following the injection. The iodized oil entered the triangular shadow, the bronchi of which were seen to be close together and to show cylindric dilatations. On October 17, the patient was doing well; however,

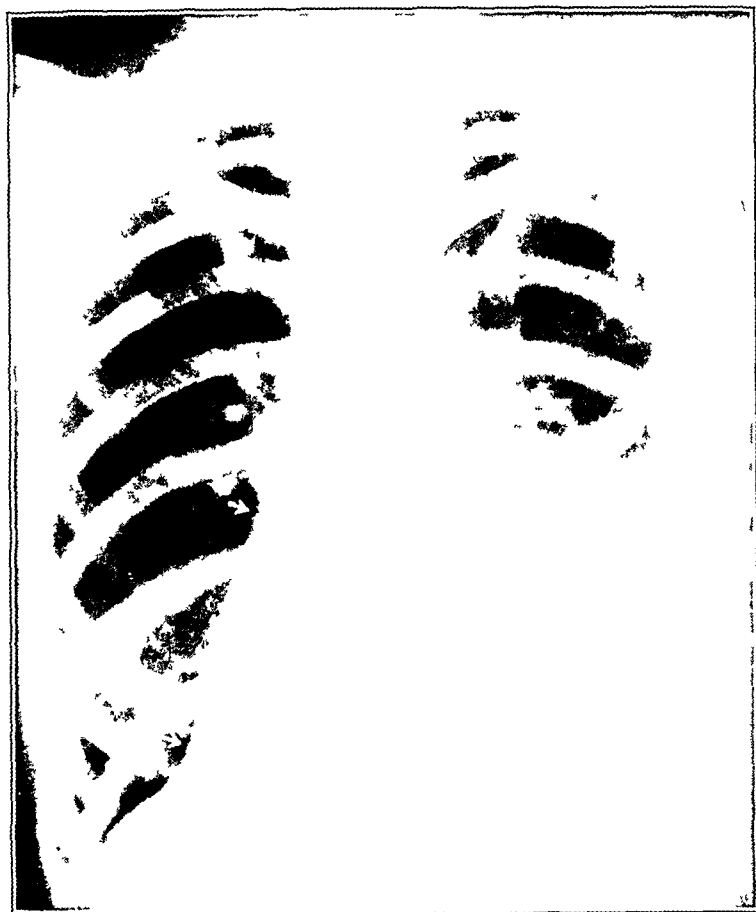


Fig. 5 (case 2).—A roentgenogram taken on Feb. 15, 1932, showing a distinct triangular basal shadow and the mediastinum again placed over toward the right. The triangular shadow is dense, small and homogeneous, and similar to that seen on September 5.

the expectoration of 2 ounces of purulent sputum a day persisted. Examination of the right side of the chest now showed few physical signs. The only remaining abnormal finding was a few medium râles. It was no longer possible to outline the triangular area clinically. Roentgen examination showed that the triangular area was much bigger and less distinct, and that it tended to be less easily differentiated from the surrounding lung (fig. 4 D). The mediastinum had definitely moved back toward the midline. Further, iodized oil injected at this time into the bronchi of the right lung demonstrated that the triangular shadow was caused by a small right lower lobe. It could be seen that the right middle and upper lobes

had enlarged and rotated so as to fill the space in the thorax normally occupied by the lower lobe. The patient improved in general health and was allowed to go home to continue postural drainage, which had been started as soon as she was well enough following the lobectomy. On discharge, she had slightly purulent sputum. This continued with occasional blood-streaking until she returned for examination on Feb. 15, 1932. She had felt quite well in the interval and had gained definitely in strength and weight. A roentgen film (fig. 5) taken at this time showed the triangular basal shadow distinctly; the mediastinum was again seen toward the right. The triangular shadow was dense, small and homogeneous, and appeared similar to the shadow seen on September 5. Iodized oil injected into the right lung again demonstrated bronchiectasis in this area, recognized as the right lower lobe.

It is seen in this case that a triangular basal shadow, representing a bronchiectatic lobe, developed in a patient known to have had bronchi of normal size six weeks previously. The right lower lobe had become bronchiectatic and so greatly reduced in size that it gave a triangular-shaped shadow on the roentgenogram. The lobe then enlarged to over twice this size in a period of only six weeks, returning to the small triangular shape during the following three months. It is inconceivable that fibrosis of the lung or a pull by contracting pleural adhesions could cause such a sudden decrease in size. The rapid expansion that took place after the small lobe was present for a few weeks could not have taken place if fibrosis had been the cause of the reduced bulk. The lobe must have decreased in size, owing to the atelectasis, which partially cleared and then returned.

It is also of interest to note that in both cases presented the atelectatic, bronchiectatic lobe was recognized clinically as a triangular area of dulness along the spinal column. In only a small percentage of cases is one able to outline the lobe clinically, but when this is possible, one finds, in addition to impaired resonance, all the other signs of consolidation, i. e., bronchial breath sounds, bronchophony and medium crackling râles. Very often, when the roentgen ray reveals a triangular shadow, one is unable to outline it clinically. A different set of physical findings produced because of atelectasis of a lobe is well illustrated by a case in which the left lower lobe was so small that it was represented by a shadow only at the hilus (fig. 6 *A*). The lobe had left the diaphragm altogether and was therefore not in the shape of a triangle. The physical findings were definitely different in the two sides of the chest. The left lower lobe was centrally placed and so small that it was impossible to find it clinically, but, owing to the over-stretched upper lobe, one noted the physical signs of a one-sided emphysema. That is, the left side gave a boxy, hyperresonant note on percussion; the breath sounds on that side were typical of emphysema, while the right side of the chest appeared normal. This case presented the smallest lobe that we have seen. Figure 6 *B* represents a roentgenogram taken after the injection of iodized oil in this case. The closely

placed, dilated bronchi are seen in the shadow near the hilus. Some of the iodized oil has entered the upper lobe, and the bronchi arising from its main bronchus are seen to go to the base in an area usually supplied by the bronchi of the lower lobe. In this particular instance, both the injection of iodized oil and the bronchoscopic examination, proved that the shadow was due to the entire left lower lobe.

As far as we are aware, no occurrence of bilateral triangular shadow in bronchiectasis has heretofore been reported. We have observed two cases showing bilateral shadows. In one, the plain roentgen appearance is shown (fig. 7 *A*). With an injection of iodized oil, the left lower

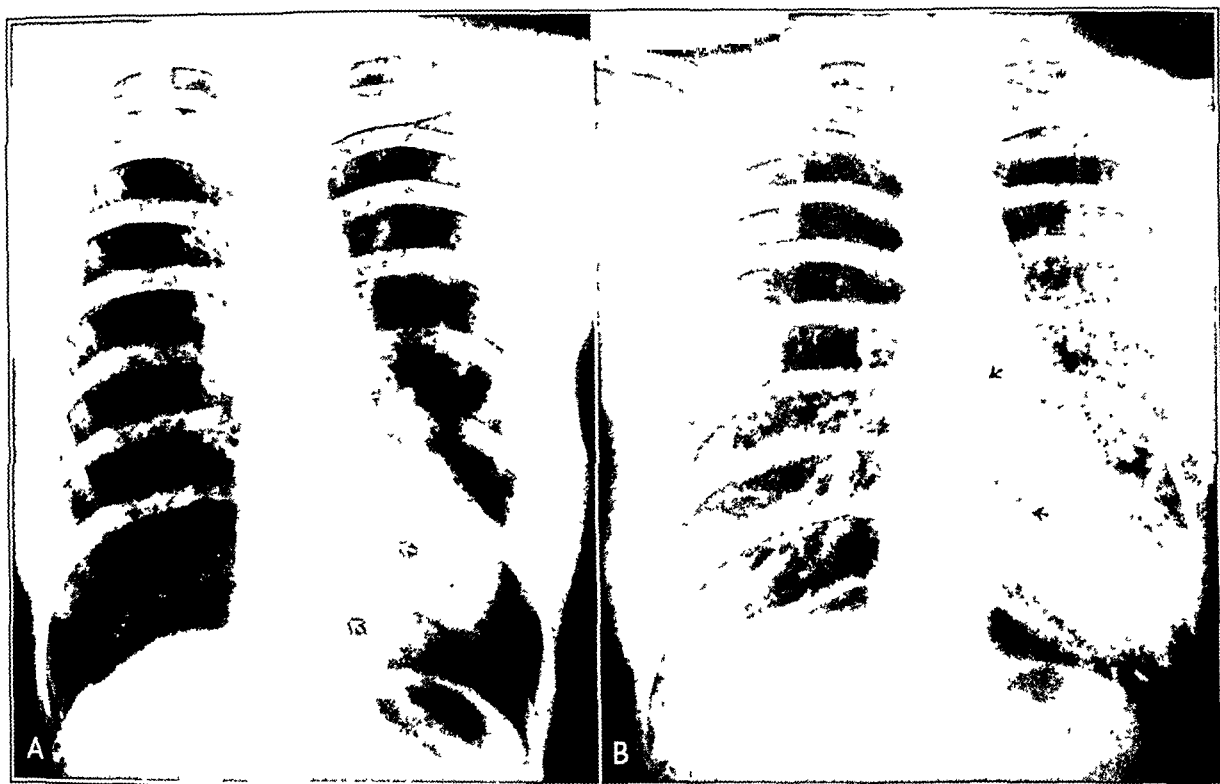


Fig. 6.—*A*, a case of atelectasis of a lobe in which the left lower lobe was so small that it was represented by a shadow only at the hilus. *B*, the same as *A*, after injection of iodized oil. The closely placed, dilated bronchi are seen in the shadow near the hilus. Some of the oil has entered the upper lobe, and the bronchi arising from its main bronchus are seen to go to the base in an area usually supplied by the bronchi of the lower lobe.

lobe was seen as a triangular shadow, the left upper lobe filling the remainder of the left hemithorax. On the right side, the right lower lobe produced the shadow, and the remainder of the right hemithorax was occupied by the right middle and upper lobes (fig. 7 *B*). In the other case of bilateral basal triangular shadow, the left-sided shadow was due to the left lower lobe, whereas the right was due to the right lower and middle lobes (fig. 8). In this case the two upper lobes were the only lobes expanded and aerated.



LOBAR ATELECTASIS, EXPERIMENTALLY PRODUCED IN  
DOGS, CAUSING A TRIANGULAR BASAL SHADOW

If, as it seemed proved, atelectasis of a lower lobe caused the lobe to become small, triangular in shape and situated as we saw it in our roentgenograms, it should be possible to reproduce the shadow in animals by causing atelectasis of the lower lobe.

In dogs, with the cooperation of Dr. Gregor McGregor of the Department of Otolaryngology, we were able completely to occlude the bronchus to a lower lobe by means of a balloon inserted through a bronchoscope. The deflated balloon was inserted and then blown up

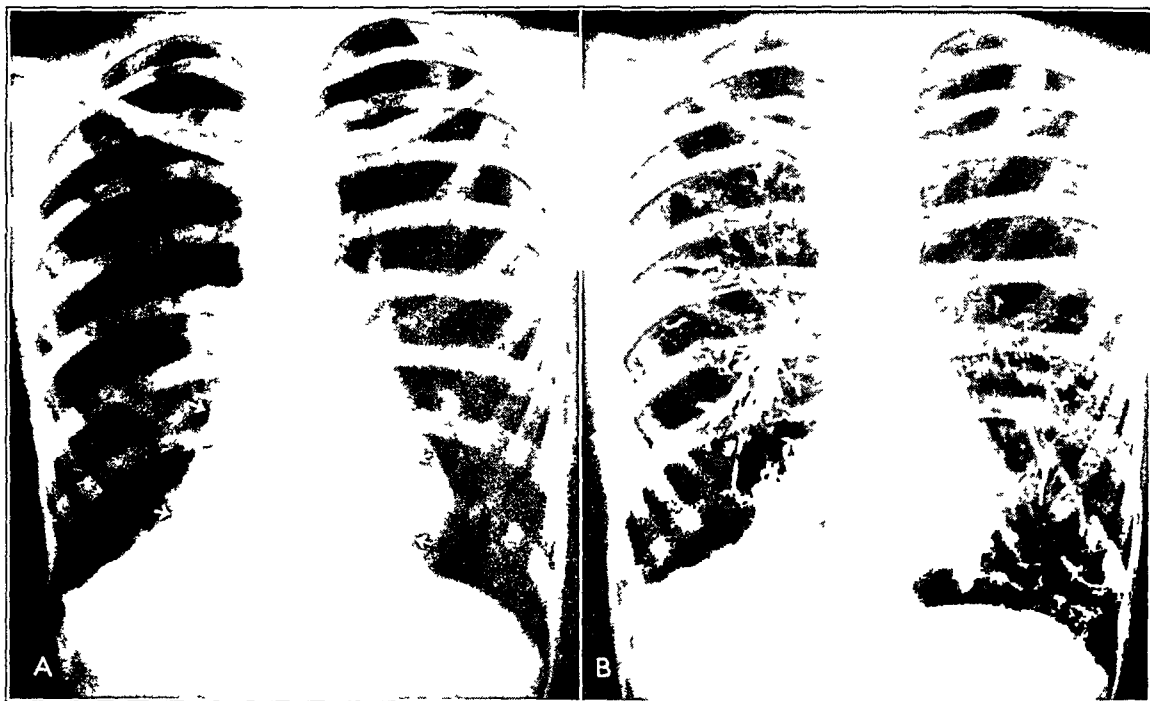


Fig. 7.—*A*, a roentgenogram showing a bilateral triangular shadow in bronchiectasis. No other instances of this condition have heretofore been reported. *B*, appearance after the injection of iodized oil. The left lower lobe is seen as a triangular shadow, the left upper lobe filling the remainder of the left hemithorax. On the right side, the right lower lobe produced the shadow, and the remainder of the right hemithorax is occupied by the right middle and the upper lobes.

so that it occluded completely the lumen of the bronchus. We found it technically very difficult to occlude the bronchus completely by means of an apparatus inserted through a bronchoscope. However, a balloon was made by which we were able to do this with regularity. Roentgenograms were made of the chests of the dogs, and under anesthesia the balloon was inserted into the bronchus to the lower lobe. The dog was allowed to come out of the anesthesia and, in the majority of cases, showed few signs of distress. At the end of twenty-four hours

the dog was again examined by roentgen rays, and in all cases in which the balloon completely occluded the bronchus of the lower lobe, a typical triangular basal shadow was seen on that side. The roentgenologic appearance of the chest was similar to that seen when a triangular basal shadow is present in man (fig. 9). The shadow itself was similar in shape and position; the mediastinum was shifted to the affected side, and the diaphragm on that side was elevated in the thorax. This appearance was present twenty-four hours after the obstruction was produced. If the animal was killed after this amount of time had

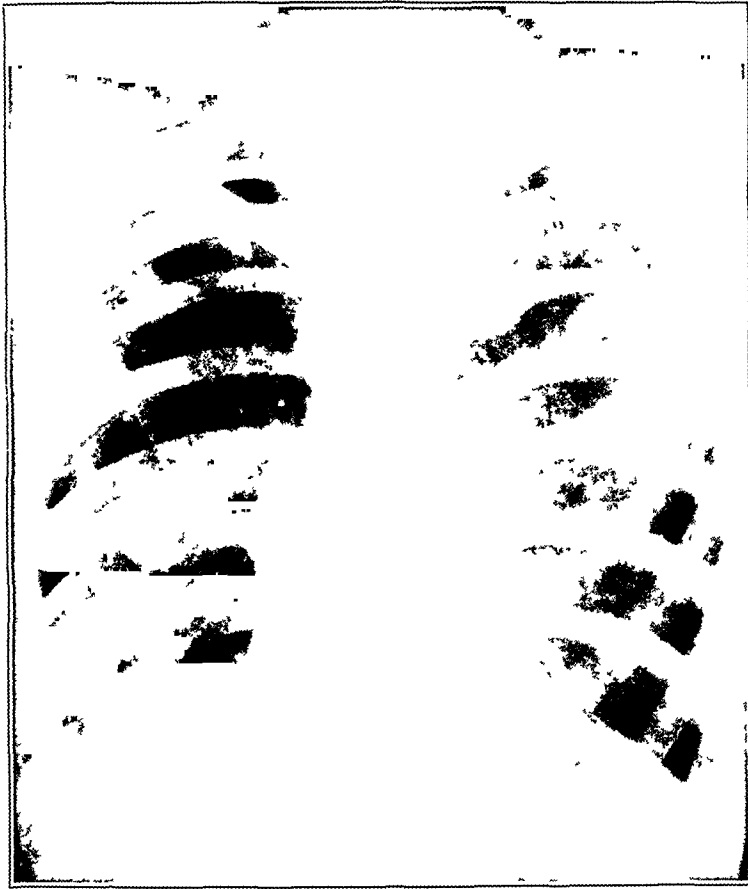


Fig. 8.—In this second case of bilateral triangular shadow, the left-sided shadow was due to the left lower lobe, whereas the right-sided shadow was due to the right lower and middle lobes. In this case the two upper lobes were the only lobes expanded and aerated.

elapsed, an atelectatic lobe was found situated in the thorax in such a position that it undoubtedly caused the triangular shadow. We were also able to remove the balloon from the bronchus through a bronchoscope at the end of twenty-four hours, after it had produced an atelectatic lobe giving a triangular shadow in the roentgenogram of the chest. Within five minutes after removing the obstruction, the lobe was seen under the fluoroscope to expand with each inspiration and to become indistinguishable from the rest of the lung. With this disappearance

of the triangular shadow, the diaphragm and mediastinum returned to their normal positions.

We were thus able to produce in dogs triangular shadows with shifted mediastinums and high diaphragms. This was done by causing atelectasis or deflation of a lower lobe by obstructing the bronchus to that lobe. The roentgenologic appearance was identical with that observed in human beings having bronchiectasis with triangular shadows. The technic employed in these experiments is not given, but



Fig. 9.—Roentgen appearance of the chest of a dog when a triangular basal shadow was created by the insertion of a balloon into the bronchus of the lower lobe.

it will be reported later when further work now being carried out on the experimental study of bronchiectasis is reported.

#### COMMENT

We believe that triangular basal shadows as described always indicate bronchiectatic lobes. Their presence in a roentgenogram of the chest warrants a provisional diagnosis of bronchiectasis, and iodized oil

should be injected to confirm this diagnosis. In every case in which one of the shadows has occurred, we have been able to prove that bronchiectasis was present. Other roentgen ray evidence of bronchiectasis is so unsatisfactory that we believe that, apart from the injection of iodized oil, triangular shadows are the best evidence of bronchiectasis that occur in plain roentgen films of the chest. They also occur frequently enough (6 per cent of our cases) to make them of real diagnostic value.

It has been shown that triangular basal shadows may be caused by atelectasis of the bronchiectatic lobe—lobar bronchiectasis—without significant fibrosis of the parenchyma of the lung or thickening of the pleura. Occlusion of the terminal bronchioles in the affected lobe from inflammatory exudate in their walls would appear to be the immediate cause of the atelectasis. It is possible for the atelectatic lobe to leave the wall of the chest and part of the diaphragm without the presence of any substance, such as air or fluid, in the pleural cavity. As the lobe becomes small and atelectatic and takes up its new position, the upper lobe expands to fill the place that it formerly occupied in the thorax. It seems unlikely that fibrosis or pleural contraction can cause the lobe to shrink and assume the shape which throws a triangular shadow on the roentgen film. If fibrosis could cause this change, one would expect to find the shadows quite frequently in a fibrosing disease, such as chronic pulmonary tuberculosis. We have not observed them in this disease. Contraction of pleural adhesions might cause the mediastinum to shift and the wall of the chest to move in. However, the lobe would be adherent to the wall of the chest and the diaphragm and could not detach itself from these and move toward the hilus. We therefore believe that atelectasis must always be the initial cause of the smallness of the lobe. Where infection occurs through the entire thickness of the walls of the bronchi in bronchiectasis, it is obvious that the infection will spread in time to the collapsed or atelectatic alveoli and may lead to fibrosis of the parenchyma, with or without pleural thickening and adhesions.

Since the time of Corrigan<sup>7</sup> and Hamilton<sup>8</sup> there have been many adherents to their theory that bronchiectasis is primarily a disease of the parenchyma, and that the bronchi are caused to dilate by the direct pull of fibrous tissue occurring in it. Sergent,<sup>5</sup> in discussing triangular basal shadows and their relationship to bronchiectasis, favored this view. We believe that the theory first advanced by Andral<sup>9</sup> and later

7. Corrigan: Dublin M. J. **13**:270, 1838.

8. Hamilton: Practitioner **22**:426, 1879.

9. Andral: Clin. méd., Paris **2**:22, 1824.

by Stokes,<sup>10</sup> that the bronchus is the structure primarily at fault in bronchiectasis, is substantiated by our observations that bronchiectasis may develop without fibrosis of the lung or pleural adhesions being present. There is ample evidence to show that in bronchiectasis the wall of the bronchus is weakened by destruction of its elastic and muscular coats.<sup>11</sup> The normal dilating force of respiration acting on the infected and weakened wall of the bronchus is probably the chief cause of the permanent dilatation found in bronchiectasis.<sup>12</sup>

#### CONCLUSIONS

1. Triangular basal shadows as seen in roentgenograms of the chest are diagnostic of bronchiectasis. Their presence should always be taken as an indication for the injection of iodized oil to confirm this diagnosis.

2. They occurred in about 6 per cent of all our cases of bronchiectasis.

3. Two cases of bilateral triangular basal shadows are reported.

4. Triangular basal shadows are caused in some cases at least, and probably in all cases initially, by a lobar atelectasis of the bronchiectatic lobe.

5. We believe that the cause of this lobar atelectasis is the plugging of the terminal bronchioles by the swelling of the bronchial wall with an inflammatory exudate.

6. Lobar atelectasis produced in dogs by completely occluding the bronchi of the lower lobes caused typical triangular shadows due to the atelectatic lower lobe.

7. Atelectatic bronchiectatic lobes may occasionally be found on physical examination; such physical findings are diagnostic of bronchiectasis.

8. Bronchiectasis may occur in the absence of both fibrosis of the pulmonary parenchyma and pleural adhesions.

Various departments aided in this work. Dr. Gregor McGregor, of the department of otolaryngology, and Dr. A. C. Singleton, of the department of radiology, were of particular assistance.

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# INTRA-UTERINE RHEUMATIC HEART DISEASE

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Intra-uterine rheumatic fever is so rare that it is considered a historical curiosity,<sup>1</sup> and Abbott,<sup>2</sup> though she was of the opinion that rheumatic endocarditis might be transmitted from the mother to the embryo, mentioned that up to the present time there is no direct proof.

In 1882, Pocock<sup>3</sup> described a case of rheumatic fever in a new-born, premature infant, whose mother was suffering from the same infection at the time of delivery. Thirty hours after birth the infant disclosed symptoms which led to a prompt diagnosis and treatment with sodium salicylate. The child recovered, and mention is made that there was no detectable damage to the heart.

In the case reported by Schaefer,<sup>4</sup> in 1886, the mother had rheumatic fever five days prior to delivery. When the child was 3 days old, it also had rheumatic fever which persisted for two months and followed a typical course. The child was treated with salicylates, and no cardiac damage was noted.

In 1888, Guthrie<sup>5</sup> reported a case in which the mother showed symptoms of rheumatic fever three days after delivery, and the child, when it was 11 days old. The joints were reddened and swollen and yielded to treatment with alkalis. There was no mention of the condition of the heart.

In the case described by Ferguson,<sup>6</sup> in 1893, the mother suffered a severe attack of rheumatic fever which persisted from the second

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From the Departments of Cardiology, White Cross Hospital and Children's Hospital.

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2. Abbott, Maud E., in Nelson Loose-Leaf Living Medicine, New York. Thomas Nelson & Sons, 1929, vol. 4, chap. 4, part 2, p. 220.

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month of her pregnancy until delivery. She gave birth to a living child apparently suffering from rheumatic fever. This diagnosis was made because of the maternal history, the distressing cry of the infant on being moved and the characteristic temperature curve. Postmortem examination revealed the heart to be normal.

#### REPORT OF A CASE

*History.*—The mother had had recurrent attacks of rheumatic fever since she was 12 years of age. Eight years following the onset, she suffered a severe attack during which she was told that she had heart disease. At the age of 25 she became pregnant and gave birth to the patient, a full-term boy. Throughout this entire pregnancy and at the time of delivery the mother had active rheumatic fever with an elevated temperature and red, swollen, painful joints. During another pregnancy, two years later, she died, undelivered, of heart failure associated with an attack of rheumatic fever.

The patient was born with red, painful, swollen joints which caused him to cry out when gentle passive motion was attempted. These observations were attested by the father and the attending physician, Dr. E. C. Beam, of Columbus, Ohio, who also heard abnormal heart sounds and recognized the presence of a cardiac pathologic process on his first examination, which was made thirty minutes after the infant's birth. The diagnosis of rheumatic fever with rheumatic heart disease was made, and the patient remained under the care of this physician until 1929, when he was referred to our clinic. The child had had dyspnea since birth, and there was evidence of heart failure during a mild tonsillitis and measles in 1928. At the age of 6 months the symptoms in the joints disappeared, and from that time there were no manifestations of active rheumatic fever.

*Examination.*—The patient was a fairly well developed white boy, who weighed 58 pounds (26,300 Gm.) and was 9 years of age. There was slight cyanosis of the lips and fingers, and moderate dyspnea and orthopnea were present. The veins in the neck were congested, and marked swinging pulsations were seen over the carotid arteries. A marked pulsation was noted over the xiphoid process, but the apex beat was diffuse and in the fifth and sixth interspaces 8 cm. to the left of the midsternal line. There was a marked thrill at the apex, which was also felt in the fourth interspace to the right of the sternum. The cardiac dulness was as follows: The left border was 10 cm. to the left of the midsternal line in the fifth and sixth interspaces, and 6 cm. to the left of this line in the third interspace, while the right border was 5 cm. to the right of the midsternal line in the fourth interspace.

A loud, rough diastolic murmur was heard at both the aortic and the pulmonic areas, and at the mitral area there was a soft blowing murmur heard through a flat first sound; there was also a rough diastolic murmur present. At the tricuspid area there was a soft blowing systolic murmur and a rough diastolic murmur. The heart rate was 112, and the rhythm was regular. There were moist râles heard in the bases of both lungs, and the liver was tender and extended 3 cm. below the costal margin. The abdomen was distended owing to moderate ascites. Both the fingers and the toes revealed marked clubbing, and the edema of the feet and ankles was moderate.

The cardiac measurements by means of the orthodiagram were: longitudinal, 15.6 cm.; horizontal, 15. cm.; base, 13.4 cm.; left ventricle, 9.5 cm.; bisector, 1.7 cm.; right ventricle, 15.6 cm.; right auricle, 8.7 cm., and left auricle, 5.2 cm. The

electrocardiogram (fig. 1) was interpreted as showing sinus tachycardia, myocardial insufficiency and right axis deviation. The laboratory findings were: urine, specific gravity, 1.008; urinary albumin, 50 mg.; urinary sugar, negative; Wassermann reaction, negative; blood sugar, 75 mg.; blood count, hemoglobin, 90 per cent, red blood cells, 4,500,000 and white blood cells, 8,600 per cubic millimeter.

*Course.*—The child remained in the hospital for a month and improved with rest and digitalis therapy, so that he could be discharged. During this time his only complaints were dyspnea and limited capacity for effort. His temperature did not exceed 98.4 F., and his respirations were from 20 to 32.

The clinical diagnosis was: rheumatic heart disease, hypertrophy and dilatation, myocardial insufficiency, panvalvulitis, mitral stenosis and insufficiency, tricuspid stenosis and heart failure with fourth degree function.

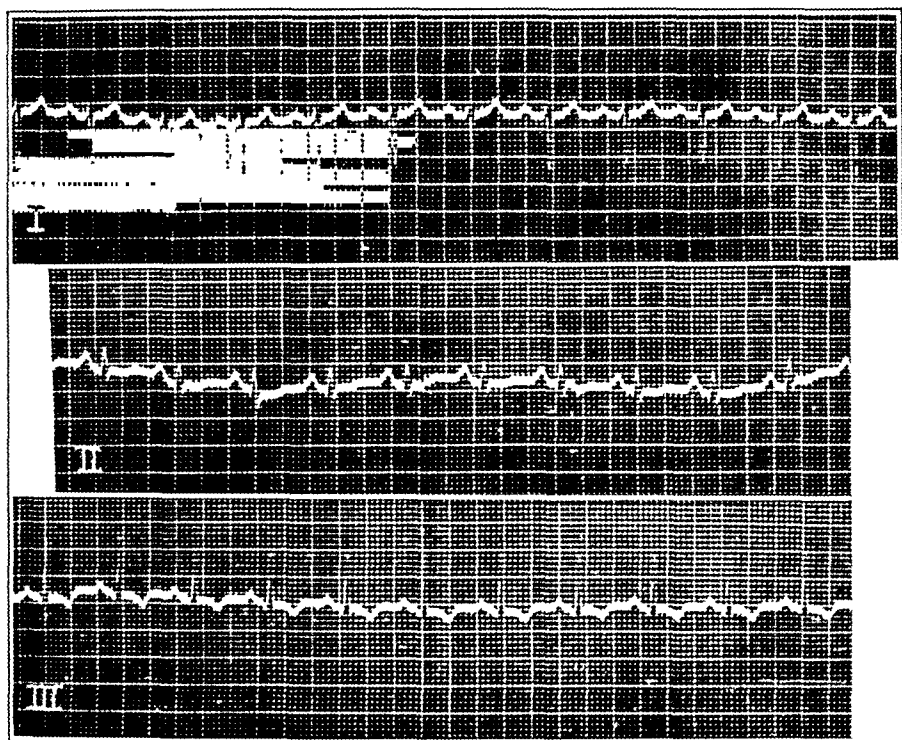


Fig. 1.—Electrocardiogram interpreted as disclosing sinus tachycardia, myocardial insufficiency and right axis deviation.

Six months later the child was again admitted to the hospital because of heart failure and with essentially the same findings, except that the cyanosis, dyspnea and orthopnea were more severe. At this time the edema extended to the knees, and the ascites was increased. The child did not respond to rest and digitalis therapy, and abdominal paracentesis had to be repeatedly performed. On Dec. 18, 1929, he died suddenly following this procedure.

*Autopsy* (Dr. R. S. Fidler).—Autopsy was performed thirty minutes after death. The body, which was not embalmed, was that of a well developed white boy about 10 years of age. There was marked edema of the entire body; especially noticeable were a large barrel-shaped abdomen and marked bilateral edema of the legs. There was edema of the prepuce, which formed a mass the size of a large walnut. The trocar puncture wound of a recent paracentesis was found approximately in the midline of the abdomen just above the pubis.



On incision through the skin and tissues of the thorax and abdominal wall, a marked subcutaneous edema was found. About 5 liters of a clear, straw-colored fluid, which coagulated on standing, filled the abdominal cavity, and each pleural cavity contained about 600 cc. of a similar fluid. The liver was enlarged and extended 2 cm. below the costal margin. The kidneys were normal in size; the capsule stripped easily, revealing a smooth, normal cortex, and on cut section the

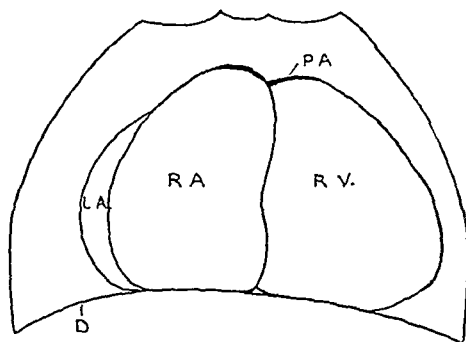


Fig. 2.—Diagram of the front view of the heart in the thorax: *P. A.*, pulmonary artery; *R.V.*, right ventricle; *R.A.*, right auricle; *L.A.*, left auricle; *D.*, diaphragm.



Fig. 3.—View of the heart showing the small opening in the pulmonary valve.

markings were well defined. The remaining viscera of the abdomen presented no noteworthy pathologic process.

On removal of the sternum, the heart was found to extend well beyond the right of the sternum, and it measured 17 cm. in the widest transverse diameter. The pericardial sac contained about 300 cc. of a clear straw-colored fluid. The parietal pericardium was smooth and glistening, except over the region of the right auricle, where it was marked with many petechial hemorrhages. Similar

hemorrhages were found on the visceral pericardium over the left ventricle. The heart had rotated to such a degree and position that the left auricle was posterior and extended to the right so as to form the right border of the heart (fig. 2). The large right auricle was in front and with the right ventricle formed the anterior surface of the heart. These two chambers gave the heart its greatly increased transverse diameter. The left ventricle was small and entirely posterior. Owing to the accumulation of fluid within the pleural cavities and the enormous size of the heart, the lungs were partly collapsed but were crepitant throughout. Permission for autopsy did not include an examination of the brain.

When the heart was empty of blood, it weighed 320 Gm. and measured 9.5 cm. across the base. The right auricle was markedly dilated, measuring 9 by 8 by 8 cm., with accompanying wide separation of the muscle bundles. The tricuspid valve was open, admitting the index finger, and the leaflets were thickened and hard, while their chordae tendineae were shortened and the papillary muscles thickened. The cavity of the right ventricle measured 4.5 by 4 cm., and the myocardium varied from 7 to 14 mm. in thickness and was firm. The pulmonary valve was closed, and its cusps were thickened and fibrous, but when forced open from below a maximum opening of 4 mm. was produced, while in width the valve measured 3.5 cm. (fig. 3). The left auricle was small; it measured 3 by 3.5 by 3.5 cm., and the wall was of uniform thickness. The mitral valve was stenosed by a thickening on the auricular surface which gave it the typical button-hole appearance. The chordae tendineae were shortened and the papillary muscles thickened. The left ventricle was relatively small with a cavity measuring 3.5 by 2 cm., and the wall was 9 mm. in thickness with a firm myocardium. The cusps of the aortic valve were moderately thickened, so that when the valve was closed an opening 2 mm. in diameter remained. The entire valvular area measured 2.5 cm. in width. The aorta was smooth with both coronary orifices open, and dissection of these arteries revealed no noteworthy pathologic process.

Microscopic examination of the tissues from the heart revealed the following: The mitral valve showed many Aschoff bodies scattered throughout the fairly well vascularized scar tissue which had replaced the normal tissue and produced tremendous thickening of the leaflets. The aortic valve revealed definite fibrosis with few nuclei and no Aschoff bodies. The pulmonary valve showed thickening by the production of a loose granular tissue covering its auricular surface, and scattered throughout were mononuclear cells, but none were grouped in such a way as to suggest the formation of Aschoff bodies. The leaflets of the tricuspid valve were compact, less vascular and thickened. The ventricles showed some increase in the intermuscular fibrous tissue, which was loose in character. The right auricle revealed an Aschoff body and considerable interfibrillar scar tissue.

#### COMMENT

The case reported by Guthrie<sup>5</sup> is frequently cited in the consideration of intra-uterine rheumatic fever, but it cannot enlighten the subject, as the mother did not have rheumatic fever until three days after delivery, and the child contracted the disease when 11 days old. In the other three cases mentioned, all the mothers had rheumatic fever at the time of delivery; in the case reported by Ferguson, the child had the disease at birth; in the case reported by Pocock, the condition was recognized within thirty hours, and in that reported by Schaefer, it developed three

days after birth. There was no cardiac damage found in any of these cases; the case reported by Ferguson was the only one in which an autopsy was performed. An analysis of these cases reveals evidence that supports the probability of intra-uterine transmission of rheumatic fever but does not prove that it can occur.

The case herein reported describes a child who was born with active rheumatic fever and a cardiac lesion, and whose mother had suffered from this disease throughout her pregnancy. These facts were affirmed by the husband and the attending physician, and at the autopsy nine years later the heart disease was demonstrated to be rheumatic with no evidence of congenital anomalies. Therefore it is obvious that the intra-uterine transmission of rheumatic fever and heart disease is not only probable, but possible.

#### SUMMARY

A case of intra-uterine rheumatic fever is reported.

It is evident from the analysis of this case that rheumatic heart disease can occur before birth.

Autopsy revealed the right side of the heart to be greatly dilated and it had rotated in such a manner that the left auricle formed the right border of the heart.

# ADIPOSITY OF THE HEART

A CLINICAL AND PATHOLOGIC STUDY OF ONE HUNDRED AND  
THIRTY-SIX OBESE PATIENTS

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The diagnosis of fatty heart was frequently made by clinicians in the past generation, but in recent years investigators have, to a large extent, avoided the problem. Considerable confusion has arisen from the use of such terms as fatty degeneration, fatty infiltration, fatty metamorphosis, adiposity of the heart (*cor adiposum* or *adipositas cordis*) and obesity of the heart.

In the past, two distinct conditions have commonly been confused, and both have been alluded to as fatty heart. These are (1) the state in which there is an abnormal increase in the amount of fat in the subepicardial connective tissue and in which penetration or infiltration of fat into the connective tissue lying between the muscle bundles and the muscle fibers takes place and (2) the state in which fatty changes take place within the cell (cytoplasm) and which most pathologists<sup>1</sup> believe to be the result of a diminished utilization (oxidation) of the fat normally brought to the muscle cell.

According to Pratt,<sup>2</sup> Harvey in the seventeenth century published the first observation on fatty heart; on dissecting the body of a very corpulent man he found the heart completely covered with fat (*cor adipe plane tectum*). In recording the findings at necropsy of the body of Parr, Harvey<sup>3</sup> described the heart as being large, thick and fibrous, and containing a considerable quantity of adhering fat, both in the circumference and over the septum, but he did not attribute the patient's death to this cause.

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From the Section on Cardiology, the Mayo Clinic.

1. Mallory, F. B.: *Principles of Pathologic Histology*, Philadelphia, W. B. Saunders Company, 1914, p. 677.

2. Pratt, J. H.: On the Causes of Cardiac Insufficiency, *Bull. Johns Hopkins Hosp.* 15:301 (Oct.) 1904.

3. Harvey, William: *Anatomical Examination of the Body of Thomas Parr*, in Harvey, William: *Works of William Harvey*, translated from the latin by Robert Willis, London, Sydenham Society, 1847, p. 589.

Both varieties of fatty heart, wrote Pratt, were recognized by Corvisart<sup>4</sup> and were described by Laennec,<sup>5</sup> but the first careful anatomic studies of the conditions were made by Quain<sup>6</sup> and Rokitan-sky.<sup>7</sup> One of the first recorded cases in which there was present a condition that was assumed to be fatty degeneration was the case studied and reported by John Cheyne,<sup>8</sup> in 1818. This case is of historic interest not only because it is a carefully recorded instance of fatty metamorphosis but also because it was the first case in which the peculiar type of respiration, now known as Cheyne-Stokes respiration, was described. At that time, Cheyne-Stokes breathing was thought to be almost pathognomonic of fatty heart. We believe that the clinical picture that Cheyne described was not actually that of fatty heart but that of arteriosclerosis, coronary sclerosis and probably previous hyper-tension.

Many observers now agree with the views advanced by Rosenfeld<sup>9</sup> and Herxheimer<sup>10</sup> that the fatty change that occurs within the cytoplasm of the cell, so-called fatty degeneration, is in reality an infiltrative process rather than true degeneration and is probably the result of two causes: a disturbance of cellular nutrition and toxemia. Owing to the general acceptance of this view, the term fatty infiltration is commonly used to describe the two dissimilar conditions. Because of the generally accepted view that the fatty changes which occur within the cell are infiltrative, we believe, as pointed out by Beattie and Dickson,<sup>11</sup> that an increase in the amount of fat in the subepicardial connective tissue and in the connective tissue lying between the muscle bundles and muscle fibers is best designated as adiposity of the heart. This term will be used throughout the remainder of this article.

Most of the literature of recent years deals chiefly with the fatty changes occurring within the cytoplasm of the cells, and little investi-

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4. Corvisart, J. N.: *An Essay on the Organic Diseases and Lesions of the Heart and Great Vessels*, Philadelphia, A. Finley, 1812, p. 153.

5. Laennec, R. T. H.: *A Treatise on Diseases of the Chest*, New York, S. S. and W. Wood, 1838, p. 682.

6. Quain, R.: *Fatty Diseases of the Heart*, *Med. Chir.* **33**:120, 1850.

7. Rokitansky, Carl: *A Manual of Pathological Anatomy*, London, Sydenham Society, 1852, vol. 4, p. 204.

8. Cheyne, John: *A Case of Apoplexy in Which the Fleishy Part of the Heart was Converted into Fat*, *Dublin Hosp. Rep.* **2**:216, 1818.

9. Rosenfeld, Georg: *Über die Herzverfettung des Menschen*, *Zentralbl. f. inn. Med.* **22**:145 (Feb. 9) 1901.

10. Herxheimer, Gotthold: *Über Fettfarbstoffe*, *Deutsche med. Wehnschr.* **27**:607, 1901.

11. Beattie, J. M., and Dickson, W. E. C.: *A Text-Book of Special Pathology*, London, Rebman, 1909, p. 522.

gative work has been done concerning the subject of adiposity of the heart. This is particularly true regarding the histologic pathology of these conditions. In a recent textbook<sup>12</sup> on pathology, the subject of adiposity of the heart is dismissed with one sentence, "Adipose tissue extends through the wall of the heart and appears under the endocardium," and several pages are devoted to the fatty changes that occur within the cell. In a recent book on diseases of the heart,<sup>13</sup> less than one page is devoted to the subject of fatty heart.

#### MATERIAL

One hundred and thirty-six patients on whom postmortem examinations were conducted formed the basis of this study. The only criterion utilized in our selection of material was the definite establishment of the fact that the patients were obese. In the cases selected, the increase in body weight was 13 per cent or more; the computations were made by the use of standard actuarial charts on the basis of age, sex, height and body weight.

The minimal degree of excess body weight in our cases was 13 per cent (9.1 Kg.); the maximal degree, 170 per cent (157.3 Kg.), and the average, 45 per cent (32.3 Kg.). Our minimal criterion of 13 per cent is conservative, for the accepted minimum is only 10 per cent (table 1).

Death was caused by a great variety of diseases, and we were thus able to study hearts that were presumably normal as well as those that were invaded by disease. The age of the patients ranged from 10 months to 75 years, the average age being 52.1 years. There were three children in the series—an infant aged 10 months and two boys aged, respectively, 10 and 14 years—who were excluded from the computations of the weight of the body and the heart. The distribution of the cases according to decades of life occurred in the following manner: first decade, one case; second decade, two cases; third decade, four cases; fourth decade, ten cases; fifth decade, twenty-seven cases; sixth decade, fifty-six cases; seventh decade, thirty-one cases, and eighth decade, five cases. There were ninety-four females and forty-two males, an approximate ratio of 7:3.

#### METHOD

This investigation necessitated the determination of certain basic data in all cases, in addition to the data already mentioned. It was necessary to obtain the weight and the height of the body and the weight of the heart. From these factors we derived the ratio of cardiac weight to body weight, and included the determination of the surface area of the body in our computations.

Quantitative determinations of fat of the heart muscle were made and compared with those for normal hearts of patients of normal body weight. Numerous sections of heart muscle which had been stained for fat were studied comparatively.

Special attention was given to certain clinical and associated pathologic findings that occurred with unusual regularity throughout the series. It was found advisable,

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12. MacCallum, W. G.: *A Text-Book of Pathology*, Philadelphia, W. B. Saunders Company, 1932, pp. 81, 88 and 448.

13. White, P. D.: *Heart Disease*, New York, The Macmillan Company, 1931, p. 438.

for comparative purposes, to divide our cases into groups, and they will be so considered in the remainder of this study: group 1, fifty-two cases of obesity without demonstrable evidence of heart disease; group 2, nine cases of obesity without demonstrable evidence of heart disease but with varying degrees of cardiac insufficiency; group 3, sixty cases of obesity with hypertension, and group 4, fifteen cases of obesity with miscellaneous conditions, such as nine cases of coronary sclerosis, two cases of hepatic cirrhosis, one case each of aortic stenosis, syphilitic aortitis and previous exophthalmic goiter, and one case in which there was a dilated and hypertrophied heart of indeterminate origin.

TABLE 1.—*Percentage and Actual Increase in Body Weight Above the Normal in One Hundred and Thirty-Five Cases\**

Excess Body Weight			Excess Body Weight			Excess Body Weight			Excess Body Weight		
Cases	Per Cent	Kg.	Cases	Per Cent	Kg.	Cases	Per Cent	Kg.	Cases	Per Cent	Kg.
1	13	13.6	35	..	23.2	69	42	26.8	103	58	39.5
2	..	9.1	36	..	21.8	70	..	29.5	104	59	37.3
3	14	9.5	37	..	21.4	71	..	31.4	105	60	24.5
4	..	9.5	38	32	22.7	72	43	23.6	106	..	43.2
5	15	14.1	39	..	21.8	73	44	31.4	107	..	36.8
6	..	13.2	40	..	23.6	74	..	33.6	108	62	40.0
7	16	13.2	41	33	46.4	75	..	23.2	109	64	39.1
8	17	14.5	42	..	25.0	76	45	31.4	110	66	45.9
9	..	15.9	43	..	20.5	77	..	29.5	111	67	43.6
10	18	11.8	44	34	25.5	78	..	23.2	112	..	43.2
11	19	13.2	45	35	24.1	79	..	31.4	113	68	40.0
12	21	13.6	46	..	25.0	80	..	23.2	114	69	46.4
13	22	14.1	47	..	25.0	81	..	34.1	115	..	44.5
14	..	17.7	48	..	24.5	82	47	36.4	116	..	44.5
15	23	13.6	49	..	24.5	83	..	29.1	117	70	44.5
16	24	19.5	50	36	28.2	84	48	36.8	118	72	55.0
17	..	20.9	51	..	24.1	85	48	29.5	119	74	53.2
18	25	17.7	52	..	22.3	86	51	31.8	120	75	54.5
19	..	16.4	53	37	27.7	87	52	29.5	121	77	66.8
20	..	18.2	54	..	31.8	88	..	35.0	122	78	55.9
21	..	19.1	55	..	46.4	89	53	44.1	123	79	50.0
22	..	20.0	56	..	46.4	90	..	36.4	124	..	53.2
23	..	17.7	57	38	25.5	91	..	39.5	125	81	70.9
24	26	18.6	58	..	32.7	92	..	34.5	126	83	44.5
25	..	19.1	59	..	28.6	93	..	36.4	127	..	56.8
26	27	20.0	60	..	29.5	94	54	41.8	128	84	62.3
27	..	16.8	61	..	30.0	95	..	36.8	129	87	62.3
28	28	23.6	62	39	25.5	96	..	37.7	130	89	32.7
29	28	17.7	63	..	30.0	97	55	34.5	131	96	66.8
30	29	22.7	64	..	23.5	98	..	48.2	132	100	68.2
31	..	20.9	65	..	34.5	99	56	33.6	133	101	75.0
32	30	19.5	66	40	28.2	100	..	34.1	134	103	69.0
33	..	19.5	67	41	29.1	101	57	36.4	135	170	157.3
34	31	23.6	68	..	28.2	102	..	36.4			

\* An infant, aged 10 months, was excluded.

#### NORMAL CARDIAC WEIGHTS

In order properly to interpret the weight of the heart in obesity it is necessary to know the weights of normal hearts of persons of normal stature and body weight. In 1928, one of us (Smith<sup>14</sup>) recorded such observations in one thousand cases. It was found that the average weight of the heart of the adult male was 294 Gm., whereas that of the adult female was 250 Gm.

14. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body, and of the Weight of the Heart to Age, *Am. Heart J.* 4:79 (Oct.) 1928.

A definite correlation between the weight of the heart and the weight of the body was determined; the ratio for males was found to be 0.43 per cent and that for females, 0.4 per cent. It was also found to be possible to calculate the weight of the heart from the weight of the body with an error varying from 8 to 10 per cent. In males the body weight in pounds is multiplied by the ratio 1.96 for the average, 1.5 for the minimum and 2.3 for the maximum; these ratios are applicable only for average body weights and are lower if persons are of increased body weight. For obese patients the ratios to be used are 1.5 for females and 1.6 for males.

The weight of the heart was found to increase with increases in the weight of the body. If the body weight remained stationary as the age increased, the weight of the heart did not increase with the added years. This, of course, does not apply to children.

#### STUDIES OF CARDIAC WEIGHT

*Obesity Without Other Demonstrable Evidence of Heart Disease.*—In fifty-two cases of our series, careful study of the hearts failed to reveal evidence of heart disease other than the abnormal deposition of fat, which will be considered separately in this paper. In none of the cases was there hypertension or positive evidence that hypertension had previously existed. In no instances were there any significant changes in the coronary arteries. These cases, therefore, so far as this investigation is concerned, furnish basic data relative to the weight of the heart in obesity.

The minimal degree of excess body weight was 13 per cent (13.6 Kg.), and the maximal, 103 per cent (69 Kg.), while the average increase was 43 per cent (29.5 Kg.). The average age of the patients was 49.3 years; the youngest was 10 months of age, and the oldest, 72 years. The cases were distributed in the various age periods as follows: first decade, one case; second decade, two cases; third decade, two cases; fourth decade, four cases; fifth and sixth decades, each sixteen cases; seventh decade, nine cases, and eighth decade, two cases. There were thirty-five female patients and seventeen male patients, a ratio of 2:1.

The average ratio of cardiac weight to body weight for the group was 0.38 per cent, whereas that for male patients was 0.41 per cent, and that for female patients, 0.35 per cent. These ratios are definitely less than those obtained when persons are of normal body weight (males, 0.43 per cent; females, 0.4 per cent).

Owing to the fact that this group of patients is small, we deem it advisable to utilize the average ratio of cardiac weight to body weight, instead of using the ratios differentially, as they occur according to sex.

The ratio of cardiac weight to body weight was less than 0.38 per cent in thirty cases (58 per cent), exactly 0.38 per cent in three cases



(6 per cent) and more than the average in nineteen cases (36 per cent). The range extended from 0.22 to 0.55 per cent (table 2).

The actual cardiac weights in this group revealed interesting data. The average cardiac weight was 376 Gm., a great increase over the

TABLE 2.—*Data Pertaining to Cardiac Weight and Body Weight in Fifty-Two Cases of Obesity Without Demonstrable Evidence of Heart Disease*

Age, Years	Sex	Ratio of Cardiac Weight to Body Weight	Height, Cm.	Body Weight, Kg.	Cardiac Weight, Gm.			Surface Area, Square Meters
					Actual	Calcu- lated	Variation	
10 mos.	F	0.22	64	11.4	25	38	—13	
59	F	0.29	163	136.4	395	450	—55	2.31
59	F	0.29	157	92.3	268	305	—37	1.92
38	F	0.30	178	113.6	345	375	—30	2.30
45	F	0.30	154	98.2	292	324	—32	1.94
63	F	0.30	163	88.6	262	293	—31	1.93
35	F	0.31	169	113.6	357	375	—18	2.20
46	F	0.32	143	86.4	280	285	—5	1.74
49	F	0.32	163	93.2	295	308	—13	1.97
42	M	0.32	175	131.8	415	464	—49	1.75
50	F	0.33	165	100.5	329	332	—3	2.06
37	F	0.34	161	90.9	307	300	+7	1.93
60	F	0.34	165	96.9	326	320	+6	2.02
50	F	0.34	167	100.0	310	330	—20	2.09
40	F	0.34	163	84.1	284	278	+6	1.88
57	F	0.35	159	95.5	350	315	+35	1.96
44	F	0.35	169	95.0	331	314	+17	2.04
57	F	0.35	171	94.5	331	312	+19	2.06
72	F	0.35	156	109.1	388	360	+28	2.04
43	F	0.36	163	82.7	296	273	+23	1.87
45	M	0.36	183	118.2	425	416	+9	2.37
53	F	0.36	161	100.0	330	300	+30	2.01
57	F	0.36	162	81.8	290	270	+20	1.86
62	F	0.36	167	127.3	450	420	+30	2.30
50	F	0.37	154	94.5	355	333	+22	1.91
10	M	0.37	153	57.7	215	203	+12	1.53
60	M	0.37	174	105.5	391	371	+20	2.18
51	M	0.37	179	101.8	380	358	+22	2.20
68	F	0.37	167	98.2	364	324	+40	2.06
60	F	0.37	166	93.2	349	308	+41	2.00
55	F	0.38	156	100.0	352	330	+22	1.97
49	F	0.38	167	95.5	365	315	+50	2.09
28	F	0.38	161	99.1	372	327	+45	2.00
29	M	0.39	173	94.1	367	331	+36	2.06
49	F	0.39	158	77.7	300	257	+43	1.79
65	F	0.39	168	90.9	357	300	+57	1.99
69	M	0.39	173	95.5	370	336	+34	2.09
43	M	0.41	171	115.5	470	406	+64	2.20
44	F	0.41	154	100.5	410	332	+78	1.96
43	M	0.41	172	102.3	420	360	+60	2.14
71	M	0.41	162	91.8	380	323	+57	1.95
50	M	0.41	183	118.2	484	416	+68	2.39
14	M	0.41	148	65.5	226	230	—4	1.58
52	F	0.43	169	86.4	370	285	+85	1.96
27	M	0.43	180	113.6	488	400	+88	2.31
26	F	0.44	163	108.6	482	359	+123	2.11
60	F	0.44	162	89.1	390	294	+96	1.93
51	M	0.45	172	98.2	450	346	+104	2.10
56	M	0.49	173	101.4	493	357	+136	2.14
48	M	0.52	188	106.8	551	376	+175	2.32
41	M	0.53	184	109.1	572	384	+188	2.30
56	F	0.55	152	81.8	445	270	+175	1.77

normal cardiac weights of persons of normal body weight. The average weight of the hearts of the male patients was 444 Gm., an increase of 150 Gm. over that of the normal. The average weight of the hearts of the female patients was 345 Gm., an increase of 95 Gm. over the normal. The computations exclude the three children in the group.

In calculating the cardiac weight in this series according to the formula of Smith, it was found that the actual cardiac weight was less

than the calculated cardiac weight in thirteen cases (25 per cent), and that the average ratio of cardiac weight to body weight in these cases was only 0.31 per cent. The actual cardiac weights in this group of eleven cases (two children being excluded) ranged from 268 to 415 Gm., and the average cardiac weight was 322 Gm. The latter value is 64 Gm. less than the average for the group. The data clearly demonstrate that the weights of the hearts of an appreciable proportion of obese persons is less than that demanded by the height and weight of the body. This fact in itself may be responsible to a considerable degree for the fairly common apparent circulatory inadequacy of obese persons.

In the majority of cases (75 per cent), however, the actual cardiac weights considerably exceeded the calculated cardiac weights; the average weight was 383 Gm., an average excess over the calculated average of 56 Gm. The range of actual cardiac weights was from 284 to 572 Gm. The findings indicate that the majority of obese persons, when heart disease other than abnormal deposition of fat is absent, have hearts that exceed in weight those of persons of normal body weight. The cardiac weight tends to parallel the increase in body weight to a certain point (about 104.5 Kg.), and when the body weight increases beyond this, the cardiac weight does not increase proportionately.

A correlation between average cardiac weight and surface area of the body was evident. This of course was anticipated, in view of the correlations of cardiac weight and body weight. Spreads of surface area of from 1.74 to 1.99 square meters were accompanied by an average cardiac weight of 335 Gm. In cases in which the surface area ranged from 2 to 2.19 square meters, the average cardiac weight was 376 Gm. In the surface area spreads of from 2.2 to 2.39 square meters, the average cardiac weight was 447 Gm.

The fifty-two cases just considered will be referred to hereafter as the control group.

*Obesity Without Demonstrable Evidence of Heart Disease but With Varying Degrees of Cardiac Insufficiency.*—These cases, although only nine in number, were of unusual interest to us, owing to the fact that the usual forms of heart disease were absent, yet the patients presented signs and symptoms of cardiac insufficiency. Four patients had congestive heart failure.

Analysis of this group was critical, and we believe that diseases capable of producing cardiac hypertrophy, including hypertension, were excluded. So far as it is possible for us to ascertain, the patients represented instances of varying degrees of heart failure, the result of obesity.

The youngest patient was 33 years of age, and the oldest, 74; the average age was 51.5 years. There were two men and seven women.

The average degree of excess body weight in this group of cases was 60 per cent (20.5 Kg.), considerably more than that in the previous group (43 per cent). The minimal increase in body weight was 14 per cent (9.5 Kg.), and the maximal increase was 170 per cent (157.3 Kg.).

The average ratio of cardiac weight to body weight was 0.39 per cent, a slight increase over that in the control group, but lower than the normal average established by Smith. The average actual cardiac weight in these cases was 450 Gm., or 74 Gm. more than that in the control group. The calculated average cardiac weight was 399 Gm., or 51 Gm. less than the actual average cardiac weight (table 3),

Although this group of cases was small, a definite correlation between the weight of the heart and of the body occurred, but the rela-

TABLE 3.—*Data Pertaining to Cardiac Weight and Body Weight in Nine Cases of Obesity Without Demonstrable Evidence of Heart Disease but with Varying Degrees of Cardiac Insufficiency*

Age, Years	Sex	Ratio of Cardiac Weight to Body Weight	Height, Cm.	Body Weight, Kg.	Cardiac Weight, Gm.			Surface Area, Square Meters
					Actual	Calcu- lated	Variation	
49	F	0.30	151	94.1	284	311	— 27	1.88
44	F	0.36	158	90.9	324	300	+ 24	1.92
58	M*	0.36	184	122.7	435	432	+ 3	2.41
44	F	0.37	156	90.9	339	300	+ 39	1.89
59	F	0.37	166	80.0	302	264	+ 38	1.87
74	F*	0.39	172	101.8	394	336	+ 58	2.12
33	M*	0.41	194	250.0	929	880	+ 49	3.00+
50	F*	0.42	168	127.7	532	422	+110	2.32
53	F	0.49	163	104.5	510	345	+165	2.09

\* Patients with congestive heart failure.

tively lowered cardiac weights with extreme instances of obesity, as shown in the control group, did not occur; in only one case was the actual cardiac weight less than the calculated weight. This, we believe, indicates that cardiac enlargement beyond certain limits in obesity, as well as in other conditions, results in circulatory inadequacy leading to cardiac failure. It is of interest in this connection to comment on the case of the man, aged 32 years, who weighed 250 Kg. and whose height was 194 cm. The cardiac weight of this patient was 929 Gm., whereas the calculated weight of the body was 880 Gm. (table 3). He suffered from congestive heart failure which resulted in death. This is of course an extreme example, yet it agrees in all respects with our data concerning the total series.

The following correlations between the surface area of the body and the cardiac weight occurred: from 1.8 to 1.99 square meters, 312 Gm.; from 2 to 2.19 square meters, 452 Gm.; from 2.2 to 2.39 square meters, 532 Gm., and from 2.4 to 3 square meters, 682 Gm.

*Obesity with Hypertension.*—Sixty obese patients had well marked hypertension, giving us the opportunity to study hearts that theoretically should reveal hypertrophy and to compare these data with those obtained in the control group. The average readings of blood pressure in millimeters of mercury were 175 systolic and 82 diastolic.

The youngest patient was 32 years of age, and the oldest, 74; the average age was 54.1 years. The cases occurred in the various age periods in the following manner: fourth decade, four cases; fifth decade, seven cases; sixth decade, thirty-one cases; seventh decade, seventeen cases, and eighth decade, one case. There were forty-five women and fifteen men, a ratio of 3:1.

The average degree of excessive body weight of the patients was 44 per cent (31.4 Kg.), the minimal was 13 per cent (9.1 Kg.) and the maximal was 101 per cent (75 Kg.).

The average ratio of cardiac weight to body weight was 0.45 per cent, a considerable increase over that in the control series (0.38 per cent). The ratios ranged from 0.29 to 0.77 per cent (table 4). The highest value in the control group was 0.55 per cent. The ratio of cardiac weight to body weight was below 0.38 per cent (our established normal for obese patients) in fourteen cases (23 per cent), exactly 0.38 per cent in three cases (5 per cent) and more than this value in forty-three cases (72 per cent). The average actual cardiac weight in this group was 467 Gm., an increase of 91 Gm. over the average in the control group. The lowest actual cardiac weight was 283 Gm. and the greatest weight, 807 Gm. (table 4).

These figures clearly illustrate the effect of hypertension on the heart in obesity, the cardiac weights unmistakably indicating cardiac hypertrophy of considerable degree. This fact is further emphasized when the individual cardiac weight, as well as the average cardiac weight of this group, is compared with that in the control group (tables 2 and 4).

When the actual cardiac weights in the cases of hypertension are compared with the calculated cardiac weights, the degree of hypertrophy existing becomes apparent. The average actual cardiac weight was 467 Gm., whereas the average calculated cardiac weight was 344 Gm., a difference of 123 Gm., as compared to a variation of only 39 Gm. in the control group. It is interesting to note the variations in the individual cases, as shown in table 4. A noteworthy fact is that the actual cardiac weight was less than the calculated cardiac weight in only eight cases (17 per cent), whereas in the control series the percentage was 25.

As would be anticipated, no definite correlation was evident between the weight of the heart and the increasing weight of the body in the obese patients with hypertension. In view of the fact that additional cardiac hypertrophy enters into the consideration of the cases and that the degree of cardiac hypertrophy obviously varies among individual

TABLE 4.—*Data Pertaining to the Cardiac Weight and Body Weight in Sixty Cases of Obesity with Hypertension*

Age, Years	Sex	Ratio of Cardiac Weight to Body Weight	Height, Cm.	Body Weight, Kg.	Cardiac Weight, Gm.			Surface Area, Square Meters
					Actual	Calcu- lated	Variation	
65	F	0.29	162	102.3	293	338	— 45	2.02
35	F	0.30	167	95.0	283	314	— 31	2.02
58	F	0.30	165	100.9	300	333	— 33	2.06
50	F	0.30	163	136.4	408	450	— 42	2.31
58	F	0.31	156	90.9	283	300	— 17	1.89
54	F	0.32	165	97.7	312	323	— 11	2.03
52	F	0.33	167	93.2	305	308	— 3	2.00
64	M	0.34	182	153.6	520	541	— 21	2.58
51	F	0.35	169	91.8	320	303	+ 17	2.01
61	F	0.35	160	90.9	320	300	+ 20	1.93
56	F	0.35	159	107.7	375	356	+ 19	2.06
56	F	0.36	177	114.5	416	378	+ 38	2.30
59	F	0.36	159	84.1	300	278	+ 22	1.86
44	F	0.37	169	136.4	500	450	+ 50	2.52
63	F	0.38	170	136.4	517	450	+ 67	2.39
33	F	0.38	160	94.5	360	312	+ 48	1.96
57	F	0.38	156	97.3	365	321	+ 44	1.95
49	F	0.39	159	100.5	390	332	+ 58	2.00
42	F	0.40	186	119.5	481	421	+ 60	2.41
59	F	0.40	175	90.9	366	300	+ 66	2.03
56	F	0.41	169	81.8	333	270	+ 63	1.92
56	F	0.42	165	90.9	383	300	+ 83	1.97
58	F	0.43	167	103.2	445	341	+104	2.10
53	F	0.43	162	105.0	450	347	+103	2.08
54	F	0.43	163	104.5	453	345	+108	2.02
66	F	0.43	157	104.1	450	344	+106	2.02
60	F	0.43	157	81.8	355	270	+ 85	1.82
38	F	0.44	171	95.5	421	315	+106	2.03
66	M	0.44	182	101.4	450	357	+ 93	2.21
32	M	0.44	189	127.3	590	448	+142	2.50
74	M	0.45	179	100.0	411	352	+ 59	2.19
59	F	0.45	180	100.5	448	332	+116	2.30
56	F	0.45	164	77.7	350	257	+ 93	1.83
59	M	0.45	177	105.9	475	373	+102	2.22
61	M	0.45	170	149.1	672	525	+147	2.49
50	F	0.45	171	97.3	435	321	+114	2.08
62	M	0.46	184	136.4	627	480	+147	2.53
60	M	0.47	184	109.1	510	384	+126	2.30
59	F	0.47	166	108.2	510	357	+153	2.12
67	M	0.48	175	108.2	520	381	+139	2.21
50	F	0.50	172	99.5	492	329	+163	2.11
63	F	0.50	146	72.7	365	240	+125	1.64
43	F	0.50	160	77.3	388	255	+133	1.80
48	F	0.51	158	113.6	575	375	+200	2.10
59	F	0.51	155	79.5	402	263	+139	1.78
66	M	0.51	172	100.9	513	355	+158	2.12
57	F	0.51	165	93.6	475	309	+166	1.99
61	F	0.53	178	109.1	579	360	+219	2.23
57	F	0.53	174	106.8	560	353	+207	2.20
56	F	0.56	166	98.6	552	326	+226	2.04
54	M	0.57	183	100.0	570	352	+218	2.21
52	F	0.57	166	99.5	567	329	+238	2.06
54	F	0.58	167	125.0	750	413	+337	2.29
65	M	0.59	172	109.1	638	384	+254	2.20
49	M	0.61	167	95.9	580	338	+242	2.03
68	M	0.62	188	109.1	679	384	+295	2.32
59	F	0.63	157	75.9	475	251	+224	1.75
63	F	0.65	164	125.0	807	413	+394	2.44
59	M	0.67	171	105.5	700	371	+329	2.16
42	F	0.77	158	84.1	643	278	+365	1.85

patients even of the same height and weight, parallelism could not be expected to occur. This observation enhances the validity of the correlations of cardiac weight to body weight in the control group.

The data occurred in the following manner: range of surface area from 1.6 to 1.89 square meters, 396 Gm.; from 1.9 to 2.09 square meters, 399 Gm.; from 2.1 to 2.29 square meters, 545 Gm.; from 2.3 to 2.49 square meters, 549 Gm., and from 2.5 to 2.59 square meters, 559 Gm.

*Obesity with Various Forms of Heart Disease.*—This was a miscellaneous group of fifteen cases, comprising nine cases of coronary

TABLE 5.—*Fifteen Cases of Obesity with Various Forms of Heart Disease, and Hepatic Cirrhosis*

Age, Years	Sex	Ratio of Cardiac Weight to Body Weight	Height, Cm.	Body Weight, Kg.	Cardiac Weight, Gm.			Surface Area, Square Meters
					Actual	Calcu- lated	Variation	
Coronary Sclerosis								
35	F	0.30	164	100.0	303	330	— 27	2.04
49	M	0.42	180	127.3	538	448	+ 90	2.41
68	F	0.43	159	109.1	470	360	+110	2.09
68	M	0.45	167	89.5	406	315	+ 91	1.97
23	F	0.46	152	98.2	447	324	+123	1.93
56	F	0.47	159	91.4	427	302	+125	1.93
57	M	0.49	167	134.1	657	472	+185	2.32
52	M	0.50	168	90.9	457	320	+137	2.00
75	F	0.51	160	109.1	550	360	+190	2.09
Aortic Stenosis								
66	M	0.78	176	102.3	800	406	+394	2.16
Syphilitic Aortitis								
66	M	0.58	184	159.1	922	560	+362	2.69
Previous Exophthalmic Goiter								
55	F	0.36	165	115.5	410	381	+ 29	2.18
Indeterminate								
29	M	0.51	167	120.5	615	424	+191	2.05
Hepatic Cirrhosis								
62	F	0.30	160	90.9	274	300	— 26	1.93
50	F	0.58	164	107.7	505	349	+112	2.11

sclerosis, one case of aortic stenosis, one case of syphilitic aortitis with aortic insufficiency, one case in which there previously had been exophthalmic goiter and one case of cardiopathy of indeterminate origin. There were also two cases of hepatic cirrhosis.

These cases will be briefly considered; the detailed data are presented in table 5. The average degree of excess body weight was 57 per cent (36.8 Kg.). The minimal excess was 25 per cent (17.7 Kg.) and the maximal excess was 87 per cent (62.3 Kg.).

The cases listed under coronary sclerosis were all marked examples of the disease; the degree of sclerosis was recorded as grades 3 and 4. There was no evidence of hypertension at the time of the last examination, and the average readings of blood pressure were 127 systolic and 71 diastolic. The youngest patient was 23 years of age, and the oldest,

75; the average age was 53.6 years. The patient who was 23 years of age was a woman suffering from juvenile myxedema of marked degree and who died of congestive heart failure. At the age of 4 years she had been severely ill with an unidentified infectious disease resulting in thyroiditis and evidently producing extensive arteritis of the coronary vessels. Nine patients (60 per cent) had coronary sclerosis. There were four men and five women. The average ratio of cardiac weight to body weight was 0.45 per cent, identical with that in the group with hypertension. The range was from 0.3 per cent to 0.51 per cent. The average actual cardiac weight was 473 Gm., which was 97 Gm. more than that in the control group. The minimal weight was 303 Gm. and the maximal weight, 657 Gm. The average calculated cardiac weight was 359 Gm., 114 Gm. less than the actual average cardiac weight. The remaining cases, isolated instances of disease, are detailed in table 5.

#### CERTAIN CLINICAL FEATURES

The average age of the entire group of obese patients at death was only 52.1 years, supporting actuarial data that the life expectancy in obesity is unfavorable. Only four patients attained the age of 70 or more. A marked predominance of female patients over male patients occurred, a ratio of approximately 2:1. These data also support the general belief that obesity is more common among women than among men.

The common association of cholelithiasis and obesity is well recognized, and in this series of cases the association occurred in fifty cases (37 per cent). Another disease frequently linked with obesity is diabetes mellitus, but only four cases (3 per cent) occurred in this series. Hypertension occurred in sixty cases (44 per cent). Heart disease, including the cases with hypertension, occurred in eighty-four cases (62 per cent).

As stated earlier in this paper, the patients who were investigated died from a great variety of causes, and only a few interesting facts in this connection will be considered. Death wholly attributable to heart failure occurred in only nineteen cases (14 per cent). The deaths occurred in cases in which there was associated primary cardiac disease, with the exception of three cases, which occurred in the group without demonstrable heart disease but with evidence of cardiac insufficiency.

That fatal pulmonary embolism occurred in twenty-six cases (19 per cent) is striking. This observation is in agreement with the general belief that obese patients as a rule constitute unfavorable surgical risks, and that the operative mortality in these cases is greater than the normal hazard. The tendency to circulatory inadequacy in cases of obesity, as already emphasized, may be partly contributory to the relatively high incidence of pulmonary embolism. Death resulting from pneumonia occurred in only nine cases (7 per cent).

## COMMENT

Obesity is a term applied to a general condition in which there is an undue accumulation of fat in the normal regions for storage or the fat depots of the body. The more common regions for the storage of fat are the subcutaneous connective tissues, the omentum, the mesentery, the bone marrow, the extraperitoneal tissues, the tissues about the kidneys and the orbits and, to a less extent, the connective tissue beneath the epicardium. The subepicardial space is one of the regions in which fat in moderate amount is normally deposited. When excess deposits of fat occur in the subepicardial space and penetration or infiltration of fat into the connective tissues lying between the muscle bundles and sometimes between the individual muscle fibers is observed, the condition is designated by the term adiposity of the heart.

*Distribution of Fat.*—Fat is commonly deposited over the base of the heart, over the auriculoventricular groove, around the bases of the great vessels, along the distribution of the coronary arteries, along the interventricular sulci and over the right ventricle, especially along its right border and anterior surface and at the apex. In practically all cases, more fat is deposited over the right ventricle than over the left. As a rule, the anterior surface contains more fat than does the posterior surface. An area on the posterior surface of the left ventricle, about half way between the apex and the base is, as a rule, the last area to be covered by fat. The subepicardial fat varies from slight increases above normal to extreme deposits which encase the entire heart with several layers of fat, in some portions measuring more than 2 cm. in thickness (fig. 1). In our series of cases there was an actual excess of epicardial fat in one hundred and twenty-nine cases (95 per cent). A slight increase of epicardial fat occurred in thirty-five cases (26 per cent), a notable increase of epicardial fat in seventy-seven cases (57 per cent) and an extreme increase of epicardial fat in seventeen cases (12 per cent). In six cases the amount of epicardial fat was not described in the postmortem protocols, and the hearts in these cases were not available for study. In one case the epicardial fat was normal in amount, but this heart also was not available for study.

Fat from the epicardium penetrated the muscle, and varying degrees of penetration occurred. As a rule, a correlation occurred between the excessive amount of epicardial fat and the amount of fat penetrating between the muscle bundles, but this was not uniformly true.

In all of the cases more fat was deposited in the wall of the right ventricle than in the wall of the left ventricle. In some of the extreme cases there were certain places where fat penetrated completely through the wall of the right ventricle, and fat was even deposited beneath the endocardium. In a few instances, the fat penetrated into the papillary



muscle of the right ventricle (fig. 2). As a rule, the fat penetrated the muscular walls in very irregular distribution. In some instances the line of demarcation between the cardiac muscle and the subepicardial fat was entirely obliterated. This was true only of the right ventricle. Involvement of the left ventricle was not so extensive in any instance. In a few cases, extreme deposits of fat were found on the right ventricle (fig. 3). It seems reasonable to believe that when fat is deposited in such quantities it is capable of interfering with the action of the heart.

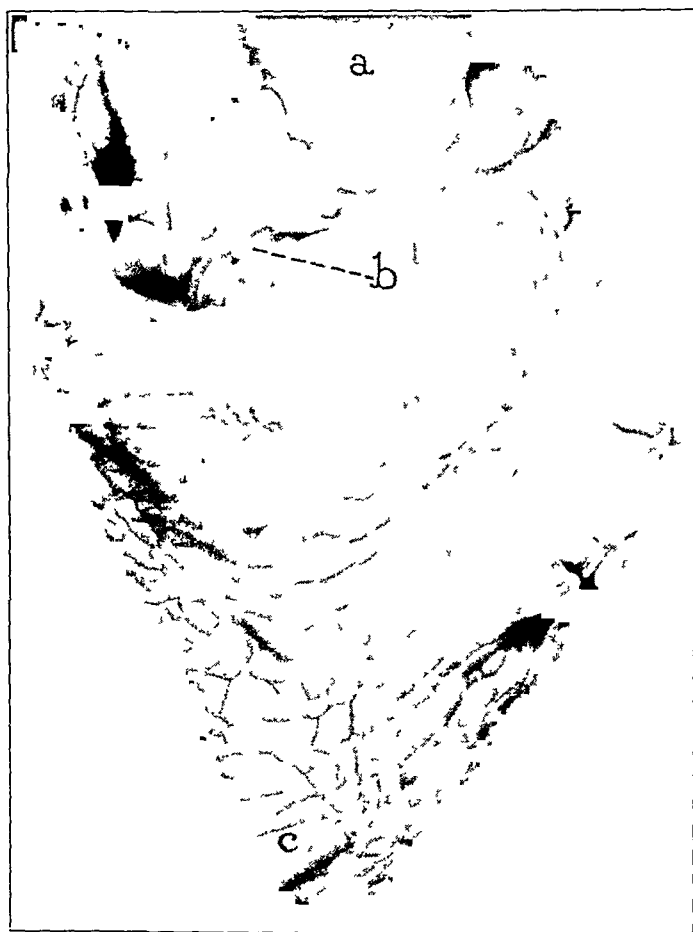


Fig. 1.—A heart that is completely encased in layers of fat, varying from one to several centimeters in thickness *a*, aorta; *b*, right coronary artery, and *c*, apex.

This extreme involvement, however, was not common. The right ventricular wall is much thinner than the left, and the same degree of penetration of fat into both walls would appear to be greater in the right. However, in almost every instance there was relatively and absolutely more fat in the right ventricle than in the left. In no instance did fat penetrate into the muscle of the left ventricle to the same degree that it penetrated into the muscle of the right ventricle, nor did we find it present in such quantities in the left ventricle as to lead us to believe

that it would in any way materially interfere with the function and activity of the left ventricle.

Observations were made on the deposit of epicardial fat and its relationship to the coronary arteries. In some instances the coronary arteries, especially the anterior descending branch of the left coronary



Fig. 2.—Cut section through the wall of the right ventricle and a papillary muscle; fat penetrating the papillary muscle may be seen. The wall of the right ventricle is indicated by *a*; the fat (black in photograph), by *b*, and the papillary muscle, by *c*. Frozen section; scarlet red stain ( $\times 9$ ).

artery, were found to lie entirely over fat; that is, the fat was situated between the artery and the cardiac muscle, and actually separated the artery from the muscle for a distance of about 2 cm. (fig. 3). In some instances the fat was deposited entirely over the artery, and in a few cases the fat was about equally deposited above and below the artery. The significance of these findings is uncertain.

In most instances a definite relationship between the excess of epicardial fat and the degree of general obesity occurred. The average excess body weight for the entire group was 32.3 Kg., and the average excess body weight in the cases in which there were extreme degrees of epicardial fat was 37.2 Kg.

Hearts which contain an excess amount of subepicardial fat are occasionally found at postmortem examination of persons who are not obese. We believe that the factors involved in the process are the same as those which occur in generalized obesity. The person has perhaps been obese at some previous time, or there may not be a sufficient deposit of fat generally to increase the body weight. No relationship was determined between the ages of the patients and the degree of epicardial fat. The hearts which contained the greatest deposits of fat were not those



Fig. 3.—A cut section of the right ventricle where the subepicardial fat is 1 cm. in thickness is indicated by *a*. The line of demarcation between the fat and the muscle is almost completely obliterated. The anterior descending branch of the left coronary artery, separated from the muscle at a distance of 1 cm., is indicated by *b*, and a cut section of the wall of the left ventricle, by *c*. The line of demarcation between the fat and the muscle is distinct. The fat has not penetrated into the muscle as it has in the right ventricle.

of the oldest persons. The degree of excess of epicardial fat did not increase with the age of the patient; this finding is at variance with an often quoted statement that old persons often have very fatty hearts. No definite relationship occurred between the degree of subepicardial fat and the basic grouping of the cases as adopted in this study. The highest percentage (40 per cent) of extremely fatty hearts occurred in the group of nine cases in which there were varying degrees of heart failure. The group of sixty cases in which there was hypertension occurred next in order, and extreme fatty deposits were noted in 27 per cent. In the group of twenty-one cases in which there were various

types of heart disease, only 14 per cent showed extremely fatty hearts, and in the group of fifty-two cases in which cardiac disease was not demonstrable, only 17 per cent showed such hearts.

Normal cardiac muscle contains considerable fat. It has been estimated that the normal amount varies from 5 to 20 per cent of the total dry weight. According to Wells,<sup>15</sup> the fat is usually held in such form that it cannot be demonstrated by stains.

Master,<sup>16</sup> in 1923, found that normal hearts contain a certain amount of microscopically visible fat within the cytoplasm of the cells, and that the mere finding of small amounts of this fat does not warrant the pathologic diagnosis of fatty degeneration. He also found that the amount of this fat (within the muscle fiber) bears no relation to the age or to the state of nutrition of the patient at the time of death.

In our series, blocks of heart muscle were taken from various parts of the left ventricular wall and were analyzed for fat by Osterberg. The amount varied from 11.6 to 23.9 per cent. The average content of fat was 15.8 per cent. In a control series of persons of normal body weight, who had normal hearts, the content of fat varied from 12 to 20 per cent. Practically the same variation occurred as in the hearts of obese patients (table 6). In blocks of muscle taken from the right ventricle, in a region that contained an extreme amount of fat, as high as 40 per cent of fat was found.

In the total series examined microscopically for fat, no instance occurred in which the intracellular fat was increased.

There is considerable difference of opinion regarding the clinical significance of the forms of fatty heart (adiposity of the heart and fatty infiltration). Some authors believe that they are common and dangerous conditions. Others believe that these conditions do not exist.

We have pointed out that two distinct and separate conditions exist, and that they are usually included under the term fatty heart. The majority of pathologic studies have been confined to the fatty changes that occur within the cytoplasm of the cells. There is considerable question whether excessive fatty changes within the cells in any way interfere with cardiac function. Welch<sup>17</sup> observed rabbits which had been kept for some time at a high temperature, and which therefore were known to have fatty changes within the cells of the heart muscle; none had symptoms of cardiac derangement either at the time of the experiment or thereafter. He also found that the cardiac fibers that

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15. Wells, H. G.: *Chemical Pathology*, Philadelphia, W. B. Saunders Company, 1920, p. 403.

16. Master, A. M.: *Fatty Degeneration of the Heart*, *Arch. Int. Med.* **31**:221 (Jan.) 1923.

17. Welch, W. H.: *Cartwright Lectures on the General Pathology of Fever*, *M. News* **52**:393, 1888.

contained an excess amount of fat within the cells contracted rhythmically. Hasenfeld and Fenyvessy<sup>18</sup> demonstrated that even when cardiac muscle was extremely fatty, following phosphorus poisoning, the cardiac action was apparently unimpaired. This fact conforms with the condition presented in figure 4, which represents a case of extreme fatty degeneration (fatty changes within the cell). The patient died of carcinoma, and there was no evidence that cardiac insufficiency had been present at any time.

We believe that the excess of fat appearing within the cytoplasm of the cell, which is presumably due to diminished utilization of the fat brought to the cell and which is found in such conditions as phosphorus and chloroform poisoning, pernicious anemia, certain cachectic diseases and some infections, seldom interferes with cardiac function. We know

TABLE 6.—Comparative Content of Fat of Heart Muscle of Twelve Obese Patients and Sixteen Patients of Normal Weight

Obese Patients			Normal Patients: Content of Fat of Heart Muscle, per Cent
Body Weight, Kg.	Overweight, per Cent	Content of Fat of Heart Muscle, per Cent	
100.5	22	11.63	12.20
250.0	170	12.09	12.92
90.9	45	12.51	13.64
122.7	39	12.92	14.08
115.5	60	13.54	14.10
88.6	25	13.56	15.30
101.8	37	13.92	16.04
125.0	83	15.36	16.69
86.4	52	17.88	17.00
90.9	48	20.70	17.63
101.4	17	21.94	18.02
127.7	78	23.90	18.43
			18.50
			19.10
			19.80
			20.62

of no instance in which it has been proved that cardiac failure has resulted from this process alone, and we know of no way to recognize it clinically. This type of fatty heart, however, is not the subject of this study.

We believe that the part played by adiposity of the heart in producing cardiac failure is, in most instances, that of adding a burden to some other disease, such as hypertension or coronary sclerosis, and that any cardiac disease is distinctly more serious if cardiac adiposity is present. In some instances, although rarely, cardiac adiposity in itself is responsible for cardiac failure.

Christian<sup>19</sup> called attention to the great vascularity of adipose tissue. A thin-walled blood capillary is visible between almost every two fat

18. Hasenfeld, Arthur, and Fenyvessy, Béla: Ueber die Leistungsfähigkeit des fettig entarteten Herzens, Berl. klin. Wchnschr. **36**:80 (Jan. 23) 1899.

19. Christian, H. A.: Some Newer Aspects of the Pathology of Fat and Fatty Degeneration, Bull. Johns Hopkins Hosp. **16**:1 (Jan.) 1905.

cells. This intimate relationship between the blood capillary system and the fat cells must be important in the metabolic functions of fatty tissue. The adipose tissue is not to be regarded as merely a passive storehouse for fat, but rather as a diffuse, fatty, vascular organ in which great synthesis or catalysis of fat may take place.

We believe that there are many factors present, both local and general, that play a part in interfering with cardiac function in the presence of adiposity of the heart. A local process may be set up by the excess deposit of fat in the subepicardial space, by penetration of fat into the connective tissue lying between the muscle bundles, in some instances between the individual fibers, and by penetration of fat into the papillary

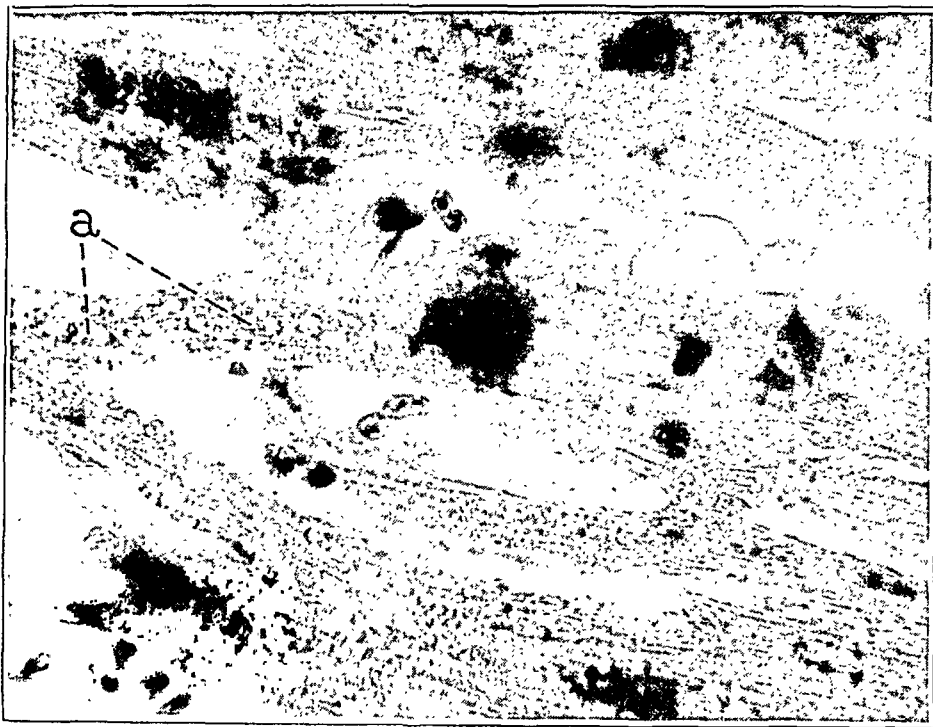


Fig. 4.—A section from the wall of the right ventricle; the fat droplets within the muscle fibers in longitudinal rows may be noted at *a*. The section is from the heart of a patient who had carcinoma of the stomach, but who had no symptoms or signs of cardiac insufficiency. Frozen section; scarlet red stain ( $\times 550$ ).

muscles. The penetration of fat may be so extreme as to interfere with the nutrition of the muscle or to impair the function of the muscle fibers. The actual separation of the muscle fibers by this excess amount of fat may interfere with myocardial function (figs. 5 and 6).

The effects of generalized obesity in producing cardiac impairment, we believe, are very important, and in the majority of instances this generalized effect is probably as important as the local effect, if not more so, in producing cardiac insufficiency. Generalized obesity promotes cardiac impairment by throwing an increased amount of work on the heart; there is an excessive amount of tissue to be nourished, there is

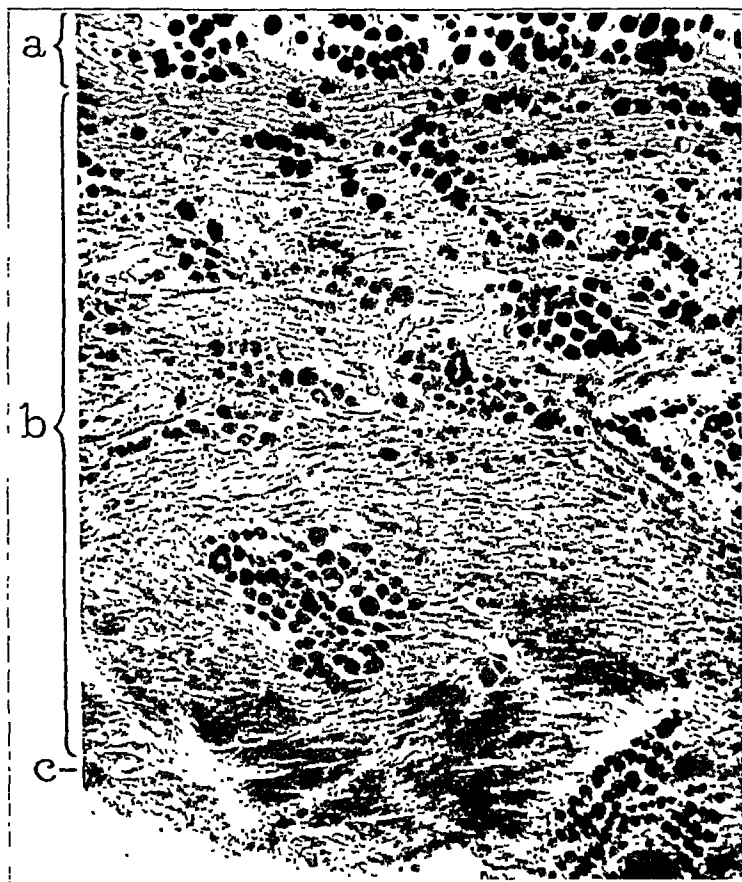


Fig. 5.—A cut section through the wall of the right ventricle. The fat shows black in the photograph. The epicardium is indicated by *a*; the wall of the right ventricle, by *b*, and the endocardium, by *c*. The fat has completely penetrated the wall. Frozen section; scarlet red stain ( $\times 32$ ).

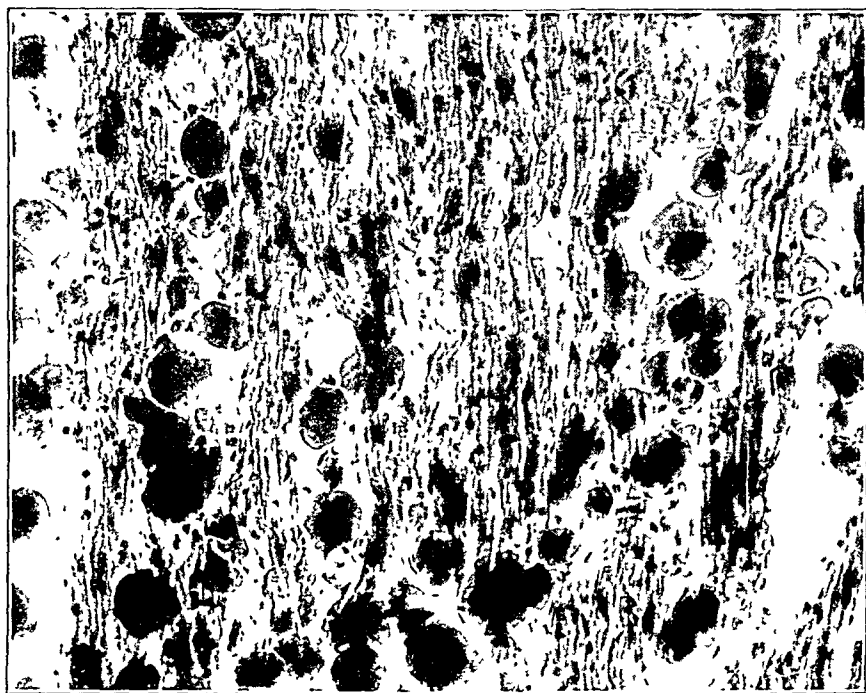


Fig. 6.—A section of the wall of the right ventricle, showing a higher magnification than that in figure 5. Frozen section; scarlet red stain ( $\times 125$ ).

an actual increase in the amount of work required in carrying around the excessive body weight, and the metabolic level of obese patients is increased.

#### SUMMARY

Doubtless many factors, both local and general, are concerned in the production of cardiac failure of obese patients. Local factors are the excessive deposit of fat in the subepicardial space and its penetration between the muscle bundles and the individual muscle fibers. There may be other factors; at all events, this excessive deposit of fat, we believe, impairs the function of the heart by its interference with cardiac activity and with nutrition of the myocardium. General factors are the increased amount of work to be performed by the heart, the excess amount of tissue to be nourished and the increased metabolism of the patients.

In obesity the weight of the heart increases and averages considerably more than that in subjects of normal weight. This increase in cardiac weight appears to be a physiologic necessity in order to permit circulatory adequacy when body weight and body surface increase. The weight of the heart keeps pace with the increasing weight of the body within certain limits, but fails to maintain this relationship in many cases in which body weight attains extreme proportions.

In a fourth of our cases of obesity in which demonstrable evidence of primary heart disease was lacking, the actual weight of the heart was less than the calculated weight, according to the formula of Smith. This observation suggests the fact that in certain cases of obesity the heart is not sufficiently large (although definitely larger than normal), and it is suggested that this status may be an appreciable factor in the apparent circulatory inadequacy so frequently evident in these cases.

When cardiac disease exists and the factor of additional cardiac hypertrophy is introduced, the correlation between cardiac weight and the increasing weight of the body is lost.

Nine cases of obesity were found in which evidence of primary cardiac disease was not demonstrable but in which symptoms and signs of varying degrees of cardiac failure occurred. Four patients had congestive heart failure, and three died of heart failure. These patients did not have hypertension, nor was there evidence that hypertension had existed previously. They were extremely obese; the average increase in body weight was 60 per cent, and the average cardiac weight was 450 Gm., only 17 Gm. less than the average in the group with hypertension.

These observations suggest the possibility that the large hearts in obesity, independent of associated pathologic changes, may occasionally fail and even result in death. However, obesity, both general and cardiac, more often is a contributory or additional factor in producing heart failure.



# INSULIN RESISTANCE IN DIABETES MELLITUS

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From the earliest days of the use of insulin in the treatment of diabetes mellitus there have been reports of cases in which larger doses were required than the clinical condition of the patient seemed to warrant. Such cases were first described by Jaksch-Wartenhorst,<sup>1</sup> Mahler and Pasterny,<sup>2</sup> Ueber and Rosenberg,<sup>3</sup> Falta,<sup>4</sup> Radoslav,<sup>5</sup> Pollak,<sup>6</sup> von Noorden and Isaac<sup>7</sup> and Matthes.<sup>8</sup> In the nine years since that time, numerous reports have revealed that in acidosis, in coma and in the presence of infection, hepatic disease or certain endocrine disorders the effectiveness of insulin may be decreased. Psychic disturbance and lack of exercise have been observed to raise the amount of insulin required. There are, however, many cases in which the poor response is unexplained.

"Insulin resistance" as the term describing relative ineffectiveness of insulin is commonly used, although there is as yet no general agreement as to its definition. Joslin<sup>9</sup> and Labbé<sup>10</sup> seem to confine its use

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1. Jaksch-Wartenhorst, R.: Insulin und Diabetes, *Zentralbl. f. inn. Med.* **45**:2 (Jan. 12) 1924.

2. Mahler, F., and Pasterny, K.: Klinische Beobachtungen über Insulin-Wirkung beim Diabetes mellitus, *Med. Klin.* **20**:337 (March 16) 1924.

3. Ueber, F., and Rosenberg, M.: Zur Diagnose und Prognose der Glycosuria innocens, *Ztschr. f. klin. Med.* **100**:655, 1924.

4. Falta, W.: Ueber einen Insulinrefraktären Fall von Diabetes mellitus, *Klin. Wchnschr.* **3**:1315 (July 15) 1924.

5. Radoslav, C. M.: Ueber die Wirkung des Insulins auf den Blutzucker beim Menschen, *Wien. Arch. f. inn. Med.* **8**:395, 1924.

6. Pollak, L.: Ueber Insulinbehandlung, *Wien. klin. Wchnschr.* **37**:55 (Jan. 17) 1924.

7. von Noorden, C., and Isaac, S.: Weitere Erfahrung über Insulinbehandlung des Diabetes, *Klin. Wchnschr.* **3**:720 (April 22) 1924.

8. Matthes, M.: Ueber Insulin, *Deutsche med. Wchnschr.* **50**:487 (April 18) 1924.

9. Joslin, E. P.: *Treatment of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1928, p. 633.

10. Labbé, M.: Existe-t-il des diabètes refractaires à l'insuline? *Bull. Acad. de méd., Paris* **97**:21 (Jan. 4) 1927; Les diabètes insulino-résistants, *Rev. belge sc. méd.* **3**:465, 1931.

to cases showing marked resistance to insulin, in which several hundred units a day are required for the elimination of glycosuria. Root,<sup>11</sup> in a recent review of the subject, calculated that a completely diabetic man should need about 200 units daily, and that a higher requirement should theoretically indicate resistance to insulin.

A broader definition of insulin resistance seems necessary, for many cases are seen in which such large doses are not required, yet the response of the blood sugar is disproportionately small. Radoslav<sup>5</sup> showed that cases of diabetes could be classed as normally insulin-sensitive, insulin-resistant or insulin-hypersensitive, according to the blood sugar curves following the administration of insulin during fasting. Discoverable complications are absent in many resistant cases. Rathery, Rudolf and T. and H. Villière<sup>12</sup> and Falta and Boller<sup>13</sup> recently reported a number of cases of resistance and commented on its frequency among their patients and the absence of demonstrable causes.

In a systematic study of over two hundred cases of diabetes in this hospital, it has been seen that relative resistance in the absence of complications is common and occurs in many patients not requiring extremely large doses of insulin. Knowledge of the degree of responsiveness to insulin has proved important in determining treatment. Five cases are reported to illustrate the method and value of distinguishing insulin-resistant from insulin-sensitive diabetes.

#### METHODS

Three methods were employed in studying these cases:

1. Determination of the ratio of the sugar excretion to the insulin requirement. The excretion of sugar per twenty-four hours is measured while the patient is receiving a standard diet of approximately 60 Gm. of protein, 160 Gm. of fat and 85 Gm. of carbohydrate. Insulin is then given in three approximately equal doses daily, and the amount required to eliminate glycosuria is determined. The relative effectiveness of the insulin may then be expressed by the ratio of the sugar excreted to the insulin required.

2. Omission test. Glycosuria is eliminated by insulin while the patient is receiving the standard diet, the regular daily requirement being determined. Then all insulin is omitted for twenty-four hours, and the resulting excretion of sugar is measured. The ratio of sugar excretion to insulin requirement gives a second method of estimating the dextrose equivalent.

3. Determination of the insulin tolerance. After the dosage necessary to keep the urine free from sugar is determined, the daily amount is gradually increased until hypoglycemic symptoms are provoked. The number of units of insulin above requirement which are tolerated without the appearance of hypoglycemia is called the insulin tolerance.

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11. Root, H. F.: Insulin Resistance and Bronze Diabetes, *New England J. Med.* **201**:201 (Aug. 1) 1929.

12. Rathery, F.; Rudolf, M.; Villière, T., and Villière, H.: Insulino-résistance dans le diabète, *Bull. et mém. Soc. méd. d. hôp. de Paris* **53**:1086 (July 22) 1929.

13. Falta, W., and Boller, R.: Insulärer und insulinresistenter Diabetes, *Klin. Wchnschr.* **10**:438 (March 7) 1931.

## REPORT OF CASES

CASE 1.—M. G., a woman, aged 41, admitted to the hospital on Oct. 3, 1930, had been suffering for six months from polyuria and increasing weakness and had lost much weight. She was emaciated and dehydrated. Her blood pressure was 125 systolic and 75 diastolic. The blood sugar during fasting was 235 mg. per hundred cubic centimeters, and she excreted 100 Gm. of sugar a day while on the standard diet. Forty-five units of insulin daily was required to eliminate glycosuria, and this amount was regularly required thereafter. When insulin was omitted for twenty-four hours, 135 Gm. of sugar was excreted. Her insulin tolerance was zero, any excess over 45 units causing hypoglycemic symptoms. If her original daily excretion of dextrose, 100 (Gm.), is divided by the insulin requirement, 45 (units), a dextrose equivalent of 2.2 is obtained. By the second method, the omission of insulin, the dextrose equivalent is 135 divided by 45, or 3.

This is a case of insulin-sensitive diabetes showing an immediate and quantitative response to treatment with or withdrawal of insulin.

CASE 2.—J. J., a man, aged 26, entered the hospital in coma on Dec. 7, 1932. He had been following a moderately restricted diet, and had been taking 70 units of insulin until three days before entry, when he had attempted to reduce the amount of insulin to save money. His blood sugar was 525 mg. per hundred cubic centimeters on entry. He received the usual treatment with large doses of insulin and moderately large amounts of carbohydrate and quickly recovered. The standard diet was then begun, and 90 units of insulin a day was required to keep the blood sugar within normal limits and prevent glycosuria. After two weeks on this regimen, insulin was omitted for one day. That the omission test is dangerous in such cases as this, with a marked responsiveness to insulin, is shown by the experience with this patient. During the twenty-four hours without insulin, the patient excreted 240 Gm. of sugar. The amount of urine rose from the daily average of 1,500 to 7,800 cc., and the patient lost 7 Kg. in weight. At the end of the twenty-four hours he was markedly acidotic and subcomatose, and the blood sugar was 480 mg. per hundred cubic centimeters. Insulin was then resumed, and the patient required 90 units daily as before. The insulin tolerance above 90 units was zero. The dextrose equivalent determined by the omission test was 2.6.

CASE 3.—M. R., a woman, aged 42, entered the hospital on Jan. 1, 1930. Four years before entry she had attacks of abdominal pain associated with jaundice. There had been no recurrences. For six weeks before admission she had increasing thirst and appetite, marked polyuria and rapid loss of weight. Physical examination showed slight obesity, a slightly enlarged heart and blood pressure of 175 systolic and 90 diastolic. The blood sugar during fasting was 638 mg. per hundred cubic centimeters, and the excretion of sugar on the standard diet was 120 Gm. daily. The glycosuria was eliminated, and the blood sugar brought within normal limits with 105 units of insulin a day. Before the omission test, the amount was gradually increased to 135 units, when mild hypoglycemic symptoms appeared four hours after the noon meal. On the day the insulin was omitted there was no sugar excreted. The patient remained in the hospital and did not receive any insulin; glycosuria did not recur during the next two weeks. She was discharged on the standard diet, without insulin.

The resistant element in this patient would probably have been missed in the ordinary routine examination, since the requirement of 105 units is not higher than that required in some insulin-sensitive

cases. The failure of glycosuria to recur after overdosage and subsequent omission of insulin suggests that perhaps resistance to endogenous insulin was broken, since a good carbohydrate tolerance developed, and exogenous insulin was not required. The original daily excretion of dextrose, 120 (Gm.), divided by 105 (units), the insulin requirement, gives a dextrose equivalent of 1.1. The dextrose equivalent by the second method (omission test) is zero divided by 105, or zero. Since there was no glycosuria when insulin was omitted and yet 135 units was required to cause hypoglycemic symptoms, the insulin tolerance was 135 units.

CASE 4.—K. P., a woman, aged 70, entered the hospital on Oct. 1, 1932, complaining of marked weakness for two months, dryness of the mouth and cramping pains in the legs. She was fairly well nourished, had moderate general arteriosclerosis and a blood pressure of 170 systolic and 80 diastolic. Laboratory studies gave normal results, except for glycosuria and a blood sugar during fasting of 375 mg. per hundred cubic centimeters. There was no fever or other evidence of infection.

The excretion of sugar on the standard diet was 62 Gm. The insulin required was 120 units. When insulin was omitted after a control period on 120 units a day, there was only 5.7 Gm. of sugar excreted. On the day of omission, the blood sugar reached only 200 mg. per hundred cubic centimeters one hour after the noon meal. Twenty-four hours later, when the dosage of 40 units before each meal had been resumed, the blood sugar was 160 mg. per hundred cubic centimeters. As in the third case, the insulin resistance was definite, although the requirement was not exceedingly high.

Insulin was gradually increased until it reached 140 units daily, when hypoglycemic symptoms appeared. It was then gradually reduced during a period of two weeks, and finally omitted, and the patient remained aglycosuric while still on the standard diet. Six weeks later an excretion of 10 Gm. of dextrose daily appeared, which was eliminated by the reduction of the carbohydrate in the diet to 50 Gm. daily. The dextrose equivalent by the first method was 0.5 and by the second method, 0.05. The insulin tolerance may be considered as 140 units, since that amount was required to cause hypoglycemia, yet its omission was not followed by glycosuria.

CASE 5.—H. P., a woman, aged 44, entered the hospital on March 18, 1930. For fifteen years she had suffered from general weakness, pruritus vulvae and furunculosis. Six years before entry, the diagnosis of diabetes was made, and she had been treated with insulin at intervals since then. For the last three years she had had attacks of precordial pain radiating down both arms.

Physical examination on entry showed marked obesity, hypertension and moderate cardiac decompensation. The heart was enlarged to the left, and there was an apical systolic murmur, a loud ringing second aortic sound and blood pressure of 178 systolic and 80 diastolic. The ankles showed considerable pitting edema. The Wassermann test of the blood was negative. The blood sugar on admission was 285 mg. per hundred cubic centimeters, and on the standard diet the excretion of sugar was 115 Gm. daily. Rapid improvement of the cardiac condition followed digitalization. The daily requirement of insulin was 120 units. An axillary abscess developed, with slight fever, and the requirement rose to 285 units, although the blood sugar during fasting at this time was only 290 mg. per hundred cubic centi-

meters. Insulin was omitted for twenty-four hours, and 112 Gm. of sugar was excreted. With more than 285 units, hypoglycemia appeared, and with less, glycosuria occurred. As the infection gradually cleared up, there was a corresponding fall in the requirement until a level of 150 units was reached. Four months later, the patient received that amount with the standard diet while being treated as an ambulatory patient, no signs of infection being present.

This case illustrates the increased resistance caused by infection in insulin-resistant diabetes. The dextrose equivalent by the first method was 0.9, and in the presence of the infection, by the omission test, was 0.4. In contrast to the patients in cases 3 and 4, who both had very high insulin tolerance, the tolerance in this case was zero.

The observations in these five cases are summarized in the table.

*Analysis of Insulin Response in Five Patients with Diabetes*

Name	Sex	Age, Years	Type of Diabetes	S. E. on Standard Diet*	Insulin Requirement	Insulin Before Omission	S. E. When Insulin Was Omitted	Dextrose Equivalent (1)†	Dextrose Equivalent (2)†	Insulin Tolerance	Insulin Requirement at Discharge	Comment
M. G.	F	41	Sensitive	100	45	45	135	2.2	3.0	0	45	Emaciated; B. P., 125/75
J. J.	M	26	Sensitive	...	90	90	240	...	2.6	0	90	Slender, under nourished; B. P., 120/70
M. R.	F	49	Resistant	120	105	135	0	1.1	0	135	0	Moderately obese; B. P., 175/90
K. P.	F	70	Resistant	62	120	140	5.7	0.5	0.05	140	0	Obese, arteriosclerosis; B. P., 170/80
H. P.	F	44	Resistant	115	120 (285)‡	... (285)	... (112)	0.9	... (0.4)	0	150	Obese; B. P., 178/80

\* S. E. indicates sugar excretion in grams per twenty-four hours.

† Dextrose equivalent: (1) by excretion; insulin requirement ratio; (2) by omission test.

‡ Determinations in parentheses were made while the patient had an axillary abscess.

#### CLINICAL CHARACTERISTICS

The majority of cases of diabetes are of mixed type, showing a more or less marked insulin-resistant element. Such typical cases of resistance or sensitiveness as those described are exceptional but not rare. Falta and Boller,<sup>13</sup> using the methods described, and in addition the Radoslav test, found in a study of seventy-four cases, that only thirteen were of the insulin-sensitive type, while fifty-two showed a definite insulin-resistant component. Nine showed marked insulin resistance.

There are certain clinical characteristics associated with each type. Insulin sensitivity is more frequent in the younger group, and in these patients there is more tendency to emaciation, acidosis and a progressive character of the disease. The insulin requirement is smaller, the

dextrose equivalent being high (usually from 1.5 to 5 or above). Insulin tolerance is low, a slight reduction in insulin causing glycosuria and a slight excess resulting in hypoglycemia. In this type insulin acts as true substitution therapy, to which the use of thyroxin, U. S. P., in typical cases of myxedema may be compared. Priesel and Wagner<sup>14</sup> showed that resistance is rare in children, definite sensitivity to insulin being the rule, sometimes with a dextrose equivalent as high as 5.

The resistant type occurs chiefly in the older group, and obesity and hypertension are common. There is less tendency to emaciation, acidosis and progression in the severity of the diabetes. The insulin requirement is on the average higher, and the dextrose equivalent is low, often being only a few tenths of a gram.

On the basis of tolerance to insulin, resistant cases may be divided into two groups, one having a high tolerance (as in cases 3 and 4) and the other having a low tolerance (case 5).

#### CAUSES OF INSULIN RESISTANCE

*Unexplained.*—Studies such as those of Radoslav,<sup>5</sup> showing insulin resistance in the absence of explanatory factors, have been amply corroborated. Gottschalk<sup>15</sup> recently made similar observations. Bauer and Monguió<sup>16</sup> observed that the threshold value of insulin shows considerable individual variation in both diabetic and nondiabetic patients. One-tenth unit per ten kilograms of body weight sufficed to cause a fall in blood sugar in some persons, while in others 0.5 unit per kilogram was necessary. High sensitivity to insulin in vagotonic persons and low sensitivity in those showing signs of high sympathetic tone have been demonstrated by Stamm.<sup>17</sup>

Scott and Dotti,<sup>18</sup> studying standardization of insulin in rabbits, found that individual animals may be either hyposensitive or hypersensitive when their response is compared with the average response of a considerable group of animals.

The presence of some contraregulatory mechanism which may be hyperactive in certain people seems necessary to explain insulin resistance such as that described in the cases reported here. The antagonism

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14. Priesel, R., and Wagner, R.: *Treatment of Diabetes Mellitus in Childhood*, Leipzig, Georg Thieme, 1932.

15. Gottschalk, A.: *Der Angriffspunkt der Kohlehydrate bei ihrer antiketogenischen Wirkung*, Zentralbl. f. inn. Med. **53**:776 (May 14) 1932.

16. Bauer, J., and Monguió, J.: *Ueber den Schwellenwert des Insulins*, Ztschr. f. klin. Med. **121**:476, 1932.

17. Stamm, E.: *Die Insulinempfindlichkeit des nichtdiabetischen Menschen und ihre Beziehung zum vegetativen Nervensystem*, Arch. f. Verdauungskr. **48**:104 (Aug.) 1930.

18. Scott, E. L., and Dotti, L. B.: *Insulin Dosage and Blood Sugar Changes*, Arch. Int. Med. **50**:511 (Oct.) 1932.

between insulin and the suprarenal-sympathetic system is easily demonstrable, and suggests that hyperactivity or hypersensitivity of this system may be a factor in the resistance. Simultaneous injections of epinephrine and insulin show antagonistic effects on the blood sugar. Patients with Addison's disease exhibit hypoglycemia and marked sensitivity to insulin. Postinsulin hypoglycemia is counteracted by injections of epinephrine. Clinically, the symptoms of hypoglycemia closely resemble those following an overdose of epinephrine: trembling, nervousness and sweating. Cannon<sup>19</sup> demonstrated that an increased secretion by the suprarenal medulla accompanies recovery from hypoglycemia.

Dworkin<sup>20</sup> found that bilateral extirpation of the sympathetic nerve chain renders cats permanently hypersensitive to insulin. De Takáts and Cuthbert<sup>21</sup> noted a rise in sugar tolerance in dogs, with increased susceptibility to insulin after celiac ganglionectomy, presumably due to reduction in the insulin-antagonistic activity of the suprarenal-sympathetic system. Observation of the islands of Langerhans in vivo<sup>22</sup> has revealed constriction of the arterioles supplying the islands after intravenous injections of epinephrine or solution of pituitary. Colwell and Bright,<sup>23</sup> after demonstrating that dextrose combustion in cats can be suppressed by the continuous administration of epinephrine, concluded that ordinary diabetes mellitus may be a functional disorder of the pancreas depending on a disease of the sympathetic nervous system in which an increased secretion of epinephrine is a factor.

Despite the absence of definite proof that clinical insulin resistance is associated with hyperactivity of the suprarenal-sympathetic system, such strongly suggestive clinical and experimental evidence makes it highly probable that this is the explanation for the common type of relative resistance which I have described.

In many instances, a poor response of the blood sugar to insulin can be attributed to some complication. Such cases can be grouped as follows:

*Infection.*—Infections complicating diabetes usually necessitate increased dosage of insulin. The mechanism producing this relative

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19. Cannon, W. B.; MacIver, M. A., and Bliss, S. W.: Studies on Conditions of Activity in Endocrine Glands, *Am. J. Physiol.* **69**:46 (June) 1924.

20. Dworkin, S.: The Response of Sympathectomized Animals to Insulin, *Am. J. Physiol.* **98**:467 (Oct.) 1931.

21. de Takáts, G., and Cuthbert, F. P.: Effect of Celiac Ganglionectomy on Sugar Tolerance in Dogs, *Am. J. Physiol.* **102**:614 (Dec.) 1932.

22. Berg, B. N.: A Study of the Islands of Langerhans in Vivo with Observations on the Circulation, *Am. J. Physiol.* **95**:186 (Oct.) 1930.

23. Colwell, W. B., and Bright, E. M.: Suppression of Glucose Combustion by Continuous Prolonged Epinephrin Administration, *Am. J. Physiol.* **92**:555 (April) 1930.

resistance is as yet obscure. Williams and Dick<sup>24</sup> recently found glycosuria and lowered carbohydrate tolerance in 41 per cent of one hundred and eight nondiabetic patients with acute infectious diseases. They attributed the loss of tolerance to damage to the pancreas. Schwentker and Noel<sup>25</sup> studied the carbohydrate metabolism in children with diphtheria and in rabbits given diphtheria toxin and concluded that there is increased glycogenolysis, followed by decreased glycogenesis, owing to the suppression of the endogenous production of insulin.

Lawrence and Buckley<sup>26</sup> noted inhibition of the action of insulin by diphtheria toxin in rabbits. At necropsy there were signs of overactivity in the thyroid and suprarenal glands. Depisch and Hasenöhl<sup>27</sup> found that, when pus from metastatic abscesses or blood serum from persons with diabetes with infection was mixed with insulin, its power to lower blood sugar decreased. Subcutaneous injections of trypsin were found by Buckley<sup>28</sup> to produce insulin resistance in rabbits.

Thus, three types of explanation have been offered: toxic injury to the pancreatic islets, production of hormones antagonistic to insulin and neutralization or destruction of insulin by toxins or ferments circulating in the blood.

*Hyperthyroidism.*—Insulin-resistant diabetes in the presence of hyperthyroidism was first described by Rosenberg and Meyer,<sup>29</sup> Strauss<sup>30</sup> and Kogan.<sup>31</sup> Since then such cases have been reported frequently. Hyperthyroidism seems to work in two ways to cause insulin resistance: The liver is made more responsive to glycogenolytic impulses, the blood sugar rising and the liver glycogen becoming depleted. In addition, glycogenesis is inhibited, so that the removal of sugar from the blood is interfered with, and storage of glycogen in the

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24. Williams, J. L., and Dick, G. F.: Decreased Dextrose Tolerance in Acute Infectious Diseases, *Arch. Int. Med.* **50**:801 (Dec.) 1932.

25. Schwentker, F. F., and Noel, W. W.: Carbohydrate Metabolism in Diphtheria Intoxication, *Bull. Johns Hopkins Hosp.* **46**:259 (April) 1930.

26. Lawrence, R. D., and Buckley, O. B.: Inhibition of Insulin Action by Toxemias and Its Explanation, *Brit. J. Exper. Path.* **8**:58 (Feb.) 1927.

27. Depisch, F., and Hasenöhl, R.: Experimentelle Untersuchungen über die Insulinresistenz beim Diabetes mellitus, *Ztschr. f. d. ges. exper. Med.* **58**:110, 1927.

28. Buckley, O. B.: Effect of Subcutaneous Injections of Trypsin on the Blood Sugar and on Insulin Action, *Brit. J. Exper. Path.* **12**:13 (Feb.) 1931.

29. Rosenberg, M., and Meyer, W. B.: Klinischer Beitrag zur Pathogenese des extrainsulären "Diabetes," *Deutsche med. Wchnschr.* **5**:935 (June 5) 1925.

30. Strauss, H.: Ueber insulin-resistente Diabetiker, *Klin. Wchnschr.* **4**:491 (March 12) 1925.

31. Kogan, V.: Antagonismus und Korrelation zwischen Pankreas, Nebennieren und Hypophysis, *Ztschr. f. klin. Med.* **104**:457, 1926.



liver is much diminished. Pettavel,<sup>32</sup> and Wegelin<sup>33</sup> found livers absolutely devoid of glycogen in exophthalmic goiter.

Serio<sup>34</sup> described the disappearance of insulin resistance in a patient with diabetes after relief from hyperthyroidism. Zeckwer,<sup>35</sup> studying spontaneous resistance in rabbits, found that in two animals with marked spontaneous resistance, thyroidectomy increased the response to insulin from ten to fifteen times.

*Pituitary Disorders.*—Early in the insulin era patients with complicating pituitary disease were found to respond poorly to treatment. Falta,<sup>4</sup> Mahler and Pasterny,<sup>2</sup> Mauriac and Aubertin,<sup>36</sup> and Wemyss<sup>37</sup> described such cases. Disorders supposed to be associated with hypersecretion of the anterior lobe are frequently accompanied by hyperglycemia. Cushing and Davidoff<sup>38</sup> found glycosuria in one fourth of a series of a hundred persons with acromegaly. In eleven of forty-four collected cases which came to autopsy the patient died in diabetic coma. Cammidge,<sup>39</sup> Joslin,<sup>40</sup> and Labbé, Escalier and Dreyfus<sup>41</sup> described the insulin-resistant type of diabetes associated with acromegaly. In a case of Cushing and Davidoff, removal of a pituitary tumor caused disappearance of hyperglycemia and glycosuria.

Further confirmation of the rôle of the anterior pituitary lobe is given by many recent investigations. As hypersecretion causes less response, so hyposecretion causes exaggerated response to insulin. A patient with hypophyseal cachexia, whose case was reported by Lucke,<sup>42</sup> showed marked hypersensitivity. Houssay and Magenta<sup>43</sup>

32. Pettavel, C. A.: Weiterer Beitrag zur pathologischen Anatomie des Morbus Basedowii, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:694, 1914.

33. Wegelin, C.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 402.

34. Serio, F.: Zur Kenntnis des insulinresistenten Diabetes, Klin. Wchnschr. **10**:1998 (Oct. 24) 1931.

35. Zeckwer, I. T.: Spontaneous Insulin Resistance in Rabbits, Am. J. M. Sc. **182**:153 (Sept.) 1931.

36. Mauriac, P., and Aubertin, E.: Insulino-résistances et diabètes par neutralisation, Presse méd. **34**:1633 (Dec. 29) 1926.

37. Wemyss, H. L. W.: Diabetes Complicating Acromegaly, and Pituitrin-Insulin Antagonism, Edinburgh M. J. **34**:343 (June) 1927.

38. Cushing, H., and Davidoff, L. M.: Pathological Findings in Four Cases of Acromegaly, with a Discussion of Their Significance, Monograph of Rockefeller Institute for Medical Research, 1927, no. 22, p. 89.

39. Cammidge, P. J.: Pituitary Glycosuria, Proc. Roy. Soc. Med. (Sect. Med.) **19**:37 (Sept.) 1926.

40. Joslin,<sup>9</sup> p. 876.

41. Labbé, M.; Escalier, A., and Dreyfus, G.: Acromégalie et diabète, Ann. de méd. **29**:222 (March) 1931.

42. Lucke, H.: Hypophysäre Magersucht und Insulin, Klin. Wchnschr. **11**:1988 (Nov. 26) 1932.

43. Houssay, B. A., and Magenta, M. A.: Sensitivity to Insulin After Hypophysectomy, Rev. Asoc. méd. argent. (Soc. de biol.) **37**:389, 1924.

and Olmsted and Logan<sup>44</sup> found that hypoglycemia was much more easily provoked in animals after hypophysectomy. Falta and Högler<sup>45</sup> found that injections of anterior pituitary extract in man prevented hypoglycemia following insulin. That the resistance caused by the anterior pituitary lobe may operate in a manner similar to that suggested for the thyroid is indicated by the work of Eitel and Loeser.<sup>46</sup> They found that injections of the anterior pituitary thyrotropic hormone into guinea-pigs caused hyperthyroidism and depletion of the glycogen in the liver.

Injections of posterior lobe extract also cause insulin resistance in man, as shown by Burn<sup>47</sup> and Blotner and Fitz.<sup>48</sup>

*Suprarenal Glands.*—The probable rôle of the suprarenal-sympathetic system in so-called "unexplained insulin resistance" has been discussed. It is probable, also, that this system is concerned in the resistance of hyperthyroidism, pituitary disorders and infections. These disorders may be accompanied by increased blood sugar and depleted glycogen in the liver, as would be expected with increased secretion of epinephrine. The frequent occurrence of vascular hypertonia in insulin resistance also supports this theory.

*Hepatic Disorders.*—Leech,<sup>49</sup> Widal and co-workers,<sup>50</sup> Labbé<sup>51</sup> and Chabrol and Hébert<sup>52</sup> described cases in which disproportionately large doses of insulin were required in the presence of various hepatic disorders. In such cases it is probable that the resistance depends at least partly on the loss of the glycogenic function of the liver. Diminished tolerance to dextrose follows the reduction of glycogen in the liver.<sup>53</sup>

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44. Olmsted, J. M. D., and Logan, H. D.: Effect of Insulin on Central Nervous System and Its Relation to Pituitary Body, *Am. J. Physiol.* **66**:437 (Oct.) 1923.

45. Falta, W., and Högler, F.: Ueber das Hypophysenvorderlappenhormon, *Klin. Wchnschr.* **9**:1807 (Sept. 27) 1930.

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48. Blotner, H., and Fitz, R.: Effect of Insulin, Pituitrin and Adrenalin upon Blood Sugar Level, *J. Clin. Investigation* **5**:51 (Dec.) 1927.

49. Leech, E. B.: Bronzed Diabetes: Its Reactions to Dietetic and Insulin Treatment, *Lancet* **2**:69 (July 14) 1923.

50. Widal, F.; Abrami, P.; Weill, A., and Laudat: Action dissociée de l'insuline sur la glycosurie et l'acétonurie, *Presse méd.* **32**:253 (March 22) 1924.

51. Labbé, M.: Coma hépatique chez un diabétique acidotique, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:1560 (Nov. 14) 1924.

52. Chabrol, E., and Hébert, P.: *Paris méd.* **1**:453 (May 16) 1925.

53. Staub, H.: Untersuchungen über den Zuckerstoffwechsel des Menschen, *Ztschr. f. klin. Med.* **93**:89 (Jan.) 1922.

Himsworth<sup>54</sup> suggested that a hepatic ferment necessary to activate insulin is reduced in hepatic diseases. Boller and Uberrack<sup>55</sup> recently showed that enormous doses of insulin are often tolerated by patients having parenchymatous damage to the liver.

*Hemochromatosis.*—This disease, in which deposits of pigment in the liver and the pancreas may be marked, is frequently accompanied by insulin-resistant diabetes. Widál, Abrami, Weill and Laudat<sup>56</sup> were the first to record this association. Sheldon<sup>56</sup> found that with progressive deposit of pigment in the pancreas there is increasing severity of the diabetes. The patient of Allan and Constam<sup>57</sup> required 500 units to eliminate glycosuria, while Root's patient<sup>11</sup> required over 1,600 units daily shortly before death. In Stetson and Peter's case,<sup>58</sup> increasing glycosuria persisted despite rising doses of insulin. In hemochromatosis a diminished production of insulin and interference with the formation and storage of glycogen by the liver and muscles apparently cause the insulin resistance.

*Diseases of the Pancreas.*—Pathologic studies of the pancreas in ordinary diabetes have failed to demonstrate constant lesions, as shown by Warren.<sup>59</sup> However, in acute pancreatic disorders diabetes frequently develops.<sup>60</sup> Glycosuria may develop in cases of pancreatic malignancy. Preexistent diabetes becomes more severe, but in the absence of other complications, the response to exogenous insulin is good. There is, in other words, no true insulin resistance. Increasing doses of insulin are required because of diminished production of insulin. Root<sup>11</sup> described pancreatic carcinoma occurring in a patient with previously mild diabetes, increasing doses up to 100 units daily being required.

*Miscellaneous Conditions.*—In acidosis and coma large doses of insulin may temporarily be required. However, after proper treatment this apparent resistance promptly disappears. Umber and Rosen-

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54. Himsworth, H. P.: The Activation of Insulin, *Lancet* **2**:935 (Oct. 29) 1932.

55. Boller, R., and Uberrack, K.: Die Insulintoleranz bei Fällen von Ikterus, *Klin. Wchnschr.* **11**:671 (April 16) 1932.

56. Sheldon, J. H.: Iron Content of Tissues in Hemochromatosis, *Quart. J. Med.* **21**:123 (Oct.) 1927.

57. Allan, F. N., and Constam, G. R.: Insulin Resistance in a Case of Bronze Diabetes, *M. Clin. North America* **12**:1677 (May) 1929.

58. Stetson, R. P., and Peters, J. P.: Carbohydrate Metabolism in a Case of Hemochromatosis, *Arch. Int. Med.* **50**:226 (Aug.) 1932.

59. Warren, S.: Pathology of Pancreas in Nondiabetic Persons, *Arch. Int. Med.* **44**:663 (Nov.) 1929.

60. Bernhard, F.: Das Auftreten des Diabetes mellitus nach akuten Pankreaserkrankungen, *Klin. Wchnschr.* **10**:632 (April 4) 1931.

berg<sup>61</sup> considered all cases of renal glycosuria refractory because of the failure of the glycosuria to disappear under treatment with insulin. This is obviously a wrong use of the term, since in renal glycosuria the response of the blood sugar to insulin is normal. Cutaneous diseases may be associated with resistance to insulin, which perhaps depends on the loss of the skin as a glycogen depot. The greater carbohydrate tolerance with exercise is a matter of common observation. Conversely, a diabetic patient confined to bed will often rapidly lose tolerance. During cardiac decompensation large doses may temporarily be required, owing, perhaps, to poor absorption of insulin in the presence of edema or to congestion of the liver.

#### COMMENT

The practical advantages of distinguishing insulin-sensitive and insulin-resistant cases would seem to be numerous. In some cases, the discovery of resistance might lead to a search for, and disclosure of, an explanatory complicating factor. A better understanding of the metabolic disturbance in each case would result, making possible a more intelligent adjustment of diet and insulin. In certain cases it has been shown that the response to alterations in the diet is very different in the two types. Fat may be considerably increased in insulin-sensitive cases without an increase in the excretion of dextrose, while increased fat in the resistant type may lead to a decrease in the dextrose tolerance. Carbohydrate, on the other hand, may be considerably increased in many resistant cases without increased excretion of sugar, while in the sensitive cases larger amounts of carbohydrate immediately lead to glycosuria.<sup>62</sup> Schmidt<sup>63</sup> distinguishes "sthenic" from "asthenic" diabetes, the two groups corresponding roughly to those described as insulin-resistant and insulin-sensitive. He has shown that the dietary management should be different in the two types. Observations such as the foregoing demonstrate the fallacy of using standard general dietary formulas in all types of diabetes. Determination of the relative response of each patient to insulin should allow a better individual planning of the diet.

A large field for the combined clinical and pathologic study of diabetes is opened by the demonstration of the frequency of relative insulin resistance in uncomplicated cases. The insulin-sensitive or

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61. Ueber, F., and Rosenberg, M.: Ueber Insulinrefraktäre Zuckerausscheidungen und Klassifikation des Diabetes auf Grund seines Verhaltens gegenüber Insulin, *Klin. Wchnschr.* **4**:583 (March 26) 1925.

62. Falta, W., and Boller, R.: Ueber das Glucose-Aequivalent des Insulins, *Wien. med. Wchnschr.* **82**:1296 (Oct. 8) 1932.

63. Schmidt, R.: Klinik des "sthenischen" Ueberdruckdiabetes, *Klin. Wchnschr.* **9**:1969 (Oct. 18) 1930.

"insular" type is apparently due primarily to decreased production of insulin. Insulin resistance seems to depend on a contraregulatory factor which counteracts the effect of insulin in the body. The possibility of a pure insulin-resistant diabetes is suggested, depending entirely on increased contraregulation, possibly by the suprarenal-sympathetic system, the pancreas being normal.

Studies such as those of Warren,<sup>59</sup> who has demonstrated that any lesions found in the diabetic pancreas can be duplicated in the non-diabetic pancreas, lend support to the theory of the extrapancreatic origin of some cases of diabetes. If careful clinical observations of the responsiveness to insulin in each case were correlated with pathologic changes in the future, much light might be thrown on this subject.

#### SUMMARY

1. Attention is called to the frequency of occurrence of relative resistance to insulin in uncomplicated cases of diabetes mellitus.

2. Clinical studies of two cases of insulin-sensitive and three cases of insulin-resistant diabetes are reported.

3. In two of these patients resistance to endogenous insulin was apparently broken, an overdosage of insulin being followed by marked improvement in carbohydrate tolerance.

4. The clinical characteristics of the insulin-resistant type as distinguished from the insulin-sensitive type are outlined.

5. Reported cases of insulin resistance may be grouped as follows:

- (a) Unexplained, such as the five cases reported in this paper. Insulin resistance is usually of mild or moderate degree in this group. Hyperactivity of the suprarenal-sympathetic system is suggested as the cause of this type of resistance. Many of these patients might be termed constitutionally resistant.

- (b) Infection.

- (c) Destructive pancreatic disease.

- (d) Disorders of other endocrine glands, particularly the thyroid, pituitary and suprarenal glands.

- (e) Hepatic disorders.

- (f) Miscellaneous conditions such as acidosis, coma, diseases of the skin and cardiac decompensation.

6. The value of determining the relative responsiveness to insulin for treatment as well as for further study of diabetes is emphasized.

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# SKIN LESIONS OF PELLAGRA

## AN EXPERIMENTAL STUDY

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Nearly two hundred years ago pellagra was described as a clinical syndrome related to poverty and inadequate nutrition.<sup>1</sup> Goldberger and his associates<sup>2</sup> were able to prevent, to produce and to cure the disease by varying certain constituents in a diet administered to human beings. They finally considered the lack of vitamin B<sub>2</sub> (G), the so-called "anti-dermatitis factor," as the sole cause of the disease. At the present time some investigators<sup>3</sup> do not accept that claim, advancing the theory that a predisposing dietary lack is important in the pathogenesis of pellagra, but that a precipitating element is also necessary. I<sup>4</sup> reported in a previous publication that the cutaneous lesions of persons with pellagra improved while the patients were restricted to a so-called "pellagra-producing" diet. Since this diet consisted of such diverse foods as cornmeal, pork fat, artificially colored (synthetic) maple syrup, polished rice, corn-starch pudding and sugar, it seemed advisable to observe the cutaneous lesions of the patients limited to a diet less complex in food materials and even more deficient in vitamin B<sub>2</sub> (G).

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1. Casal, D. G.: *Historia natural y medica de el Principado de Asturias, Abra posthuma del Doctor D. G. Casal, Medico de Su Magnestad y su Proto-medicin de Castilla*, Madrid, 1762.

2. Goldberger, J.; Waring, C. H., and Willets, D. G.: The Prevention of Pellagra, *Pub. Health Rep.* **30**:3116, 1915. Goldberger, J.; Wheeler, G. A., and Sydenstricker, E.: A Study of the Relation of Diet to Pellagra Incidence, *Pub. Health Rep.* **35**:648, 1920. Goldberger, J., and Wheeler, G. A.: Experimental Production of Pellagra in Human Beings by Means of Diet, *U. S. Pub. Health Service, Hyg. Lab., Bull. no. 120*, 1920.

3. Aykroyd, W. R.: Vitamin B<sub>2</sub> Content of Cereals and Supposed Connection Between Human Pellagra and Deficiency of This Vitamin, *Biochem. J.* **24**:1479, 1930. Gurin, S. S., and Eddy, W. H.: Is Rat Dermatitis Consequent on Vitamin B<sub>2</sub> (G) Deficiency True Pellagra? *J. Exper. Med.* **54**:421, 1931.

4. Spies, T. D.: Pellagra: Improvement While Taking So-Called "Pellagra-Producing" Diet, *Am. J. M. Sc.* **184**:837, 1932.

Evidence is presented in this paper to show that the dermatitis of pellagra often improves while the patient is restricted to a diet of corn-starch and lactose.

#### EXPERIMENTAL WORK

*Materials and Methods.*—Ten patients with the characteristic dermatitis of pellagra were chosen for this experiment, and extreme care was exercised to select those without neurologic involvement. Each patient remained in bed throughout the experiment and was given a diet of corn-starch and lactose amounting to 2,000 or 3,000 calories a day. Two of the six persons in this series having stomatitis were unable to tolerate this diet and frequently vomited; the stomatitis and glossitis rapidly became worse; so the diet was discontinued. As soon as the dermatitis of the eight remaining patients healed, they were given a high caloric, high vitamin diet. In order to test this diet still further it was fed to six young albino rats.

*Observations.*—The skin lesions of the eight patients who tolerated the diet of lactose and corn-starch showed definite improvement during the first six to fifteen days of the experiment. In all respects the healing process appeared similar to that of persons with pellagra receiving an adequate diet. Each patient rapidly lost weight and strength during the experimental period, but this apparently did not affect the steady improvement of the dermatitis. The stomatitis of one person improved, and that of the three others became worse while they received the restricted diet. The four patients free from stomatitis at the beginning of the experiment did not develop it, and none of the patients in this experiment showed any signs of involvement of the central nervous system. The two patients who were unable to tolerate the corn-starch and lactose rapidly improved after the experimental diet was discontinued and a well rounded one substituted. The rats receiving the lactose and corn-starch lost weight and died within four weeks after the beginning of the experiment.

#### COMMENT

It has been shown that the cutaneous lesions of patients with pellagra improved while they were receiving a diet of corn-starch and lactose. This work confirms and somewhat extends my previous observation that persons with pellagra restricted to a diet of polished rice, corn-starch, corn-meal, pork fat, maple syrup and sugar showed marked improvement of their dermatitis. The previous "pellagra-producing" diet<sup>5</sup> and the foods used in this experiment were found inadequate for the normal nutrition of young rats. It is impossible to state whether or not the dermatitis would have recurred had the patients been restricted to either of these nonpalatable diets for an indefinite period. A satisfactory explanation for the striking improvement of the dermatitis is difficult to offer. Rest in bed may have been a contributing factor, or there may have been more essential elements in this deficient diet than in the insignificant amount of food ingested by these patients before enter-

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5. Spies, T. D., and Grant, Jean: An Experimental Study of a So-Called "Pellagra-Producing" Diet, *Am. J. Physiol.* **104**:18, 1933.

ing the hospital. Possibly these patients had begun to improve, although there was no evidence of it at the time they were first given the restricted diet. Wheeler<sup>6</sup> has suggested that the improvement of the patients receiving an inadequate diet may take place as a result of a breakdown in the body protein with subsequent healing of the lesions. It is true that each person on this restricted diet showed a loss of body weight, but without exception each had a definite history of marked loss in weight, yet with no healing of the lesions, before he was admitted to the hospital.

I,<sup>7</sup> as well as many others, have noted that the disease may involve the central nervous system, the gastro-intestinal tract and the skin in the same patient while in other patients it may affect one or two organ systems. In several instances<sup>7</sup> I have observed that the dermatitis and stomatitis healed while there was steady progression of the disease of the central nervous system. It can be seen from this experiment that too much importance may have been attached to the healing of the cutaneous lesions by some of the investigators of the past. In view of this work and of the known observations concerning the lack of uniformity of the disease in involving the various organ systems of the body, it even appears possible that the specific chemical substance related to the development of dermatitis is not the same as that affecting the other manifestations of pellagra.

#### SUMMARY AND CONCLUSIONS

1. It has been shown in this experiment that persons with pellagra tolerating a diet of lactose and corn-starch show improvement of their cutaneous lesions. This work confirms and somewhat extends my previous observation that the dermatitis of pellagra improves while the patients receive a so-called "pellagra-producing" diet.

2. It is recommended that improvement in dermatitis be interpreted with great care before accepting it either as an index of efficacious treatment or of favorable prognosis.

3. It appears possible that the specific chemical substance related to the development of the dermatitis is not the same as that affecting manifestations of the disease in the gastro-intestinal or central nervous system.

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6. Wheeler, G. A.: Results of Some Studies Dealing with Diets in Pellagra (Discussion), *South. Med. & Surg.* **94**:131, 1932.

7. Spies, T. D.: Unpublished data.



# CHANGES IN BLOOD PRESSURE OF YOUNG MEN OVER A SEVEN YEAR PERIOD

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In 1925, Sutherland and one of us (Dr. Diehl)<sup>1</sup> published an analysis of the systolic blood pressures of 5,122 male students of the University of Minnesota. The study showed that although most college students give normal blood pressure readings at all times, some have systolic pressures which are persistently above 140 mm.; others, systolic pressures persistently between 130 and 140 mm.; others, pressures intermittently above 130 mm.; and still others, pressures above 130 mm. on only one occasion. The significance of these moderate, intermittent and transient elevations of blood pressure in young persons was discussed at that time, but it was concluded that only follow-up studies over many years could finally determine whether these were unimportant or whether they represented an early stage of persistent hypertension.

We are now reporting the first of a series of follow-up studies of blood pressure in college students. In this study determinations of blood pressure were made on 155 young men all of whom had been students at the University of Minnesota from five to ten years previously. The average age of these young men at the time of their first physical examination in the university was 19.8 years, and at the time of the follow-up examination, 26.8 years. This indicates an average interval of seven years between examinations. While in college each of the men had had at least two determinations of blood pressure, and the group as a whole had averaged four determinations, all of which were made by physicians on the staff of the Students' Health Service. The follow-up examination, which usually consisted of only one determination, was made either by a member of the staff of the Health Service or by a physician in private practice.

The average of the systolic pressures of these 155 undergraduates was  $126.18 \pm 0.78$  mm. At the time of the follow-up examination seven years later, the average was  $123.97 \pm 0.57$  mm. Although the

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1. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men, *Arch. Int. Med.* **36**:151 (Aug.) 1925.

probable errors indicate that the apparent decrease in the mean pressures of the group is without significance, it is at least interesting to note that the average pressure showed no increase over this period.

#### DIVISION INTO GROUPS

For purposes of analysis the 155 subjects were divided into five groups according to their blood pressures while in college. These groups are as follows: group I, called the persistent hypertension group, composed of persons whose systolic pressures averaged 140 mm. or more; group II, called the group with moderately elevated pressures, composed of persons whose systolic pressures averaged between 130 and 140 mm.; group III, called the group with intermittently elevated pressures, composed of persons who had systolic pressures intermittently above 130 mm.; group IV, called the group with transiently elevated pressure, composed of those who gave only one reading above 130 mm., and

TABLE 1.—*Average Ages and Systolic Pressures by Groups*

	During College Years		From Five to Ten Years Later	
	Average Age	Average Systolic Pressure	Average Age	Average Systolic Pressure
Group I.....	21.71 $\pm$ 0.87	144.63 $\pm$ 1.48	29.00 $\pm$ 0.80	138.27 $\pm$ 1.48
Group II.....	19.44 $\pm$ 0.40	133.63 $\pm$ 1.58	27.19 $\pm$ 0.43	128.75 $\pm$ 1.47
Group III.....	18.71 $\pm$ 0.38	128.82 $\pm$ 0.72	27.39 $\pm$ 0.51	126.75 $\pm$ 0.51
Group IV.....	20.67 $\pm$ 0.37	124.35 $\pm$ 0.85	27.23 $\pm$ 0.31	124.89 $\pm$ 0.80
Group V.....	21.21 $\pm$ 0.44	116.13 $\pm$ 0.52	28.10 $\pm$ 0.39	116.84 $\pm$ 0.62

group V, called the normal group, composed of those whose systolic pressures were always under 130 mm.

Obviously these groupings are arbitrary and a subject's classification into one or another might change with an increase in the number of determinations which were made. However, for the purposes of this study these groupings will serve reasonably well.

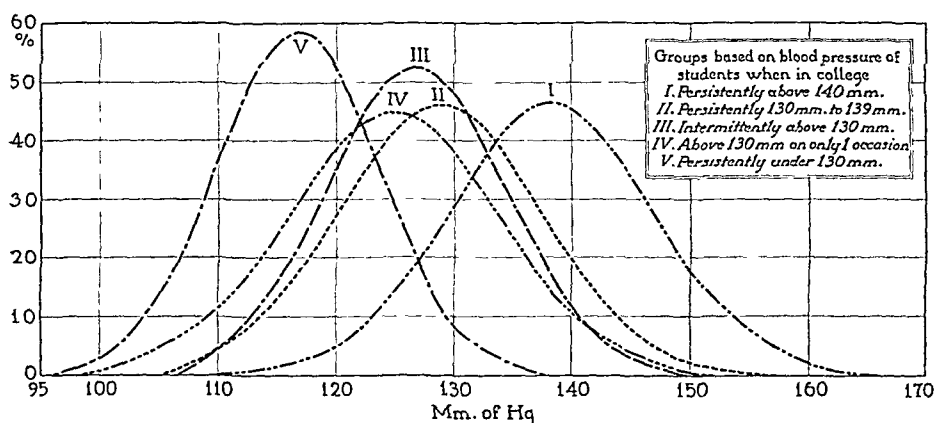
#### OBSERVATIONS

*Age.*—Table 1 shows the average ages of the groups both at the time of the original examinations and at the time of the follow-up examinations. Although the group with persistent hypertension (I) shows the highest average age and the normal group (V) the next highest average age, none of the differences in age are statistically significant.

*Group with Persistent Hypertension.*—In this group there were 15 students each of whom showed an average systolic pressure of 140 mm. or more during the years at college. Seven years later, 12, or 80 per

cent,<sup>2</sup> of these students had systolic pressures of 130 mm. or more; 8, or 53 per cent,<sup>2</sup> pressures of 140 mm. or more, and 3, or 20 per cent,<sup>2</sup> pressures of 160 mm. or more. The average pressure of the group, however, decreased from  $146.63 \pm 1.48$  mm. during the years at college to  $138.37 \pm 1.48$  mm. at the time of the follow-up study. This decrease in the average of the group is due to the fact that 3 of the men who had had a systolic pressure of 140 mm. in college gave readings of less than 130 mm. at the time of the follow-up examination.

Palmer<sup>3</sup> found in a follow-up study of 49 Harvard students who had systolic pressures of 140 mm. or more when in college that after ten years 22 per cent had pressures of over 140 mm. and 10 per cent had pressures of over 150 mm. This lower incidence of persistently high pressures in Palmer's series than in ours—22 per cent as compared to 53 per cent—is doubtless due largely to differences in the composition



Theoretical normal distribution curves of the systolic blood pressures of the several groups at the time of the follow-up study.

of the groups in which the follow-up studies were made, Palmer's hypertension group being so designated on the basis of a single physical examination in college, whereas our hypertension group contained only students whose systolic pressures in college averaged 140 mm. or more on repeated examinations.

*Group with Moderately Elevated Pressures.*—Eight, or 50 per cent of the 16 men who had systolic pressures of from 130 to 139 mm. during college years still had pressures of 130 mm. or more, and 2, or 12.5 per cent, had pressures of 140 mm. or more, seven years later. The average pressure of this group during the years at college was

2. Percentages such as these are used throughout in order to show trends. If they are to be used for other purposes, the small number of the cases on which they are based needs to be taken into consideration.

3. Palmer, Robert Sterling: The Significance of Essential Hypertension in Young Male Adults, J. A. M. A. **94**:694 (March) 1930.

133.63  $\pm$  1.58 mm., and at the time of the follow-up examination, 128.75  $\pm$  1.47 mm.

*Group with Intermittently Elevated Pressures*.—This group consisted of 24 students whose systolic blood pressures during college years were intermittently above 130 mm. At the time of the follow-up examination 9, or 37 per cent, of the students had systolic pressures of 130 mm. or more, and 2, or 8 per cent, pressures of 140 mm. or more. The average systolic pressure of the group when in college was 128.82  $\pm$  0.72 mm., and at the time of the follow-up examination, 126.75  $\pm$  0.56 mm.

*Group with Transient Elevations of Blood Pressure*.—This group consisted of 45 students, each of whom during college years showed a systolic blood pressure reading of 130 mm. or more on only one occasion. Seven years later, 13, or 30 per cent, of these students had systolic pressures of 130 mm. or more, and 2, or 5 per cent, pressures of 140 mm. or more. The average systolic pressure of these persons during their college years was 124.35  $\pm$  0.85 mm., and at the time of the follow-up examination, 124.89  $\pm$  0.89 mm.

*Normal Group*.—Fifty-five men whose systolic blood pressure during their undergraduate years was always below 130 mm. were reexamined, and only 2, or 4 per cent, of them had pressures of over 130 mm.; none had a pressure as high as 140 mm. Palmer reports that in 66 Harvard men whose blood pressures had been normal when in college reexamination after ten years revealed that 4.5 per cent had systolic pressures between 140 and 150 mm., and that 1 had a pressure of over 150 mm. Here again the differences between our results and Palmer's are doubtless due to differences in the composition of the groups studied, or, to be more specific, to different definitions of "normal."

#### COMMENT

Various studies of blood pressure have indicated that most of the elevations observed in young persons are transient and are due largely to nervousness and excitement at the time of examination. Whether these transient or recurrent elevations of blood pressure produce strain on the cardiovascular system which eventually leads to persistent hypertension is an important question and one on which there has been much difference of opinion. The results of this study indicate that young men who show persistent, intermittent or even transient elevations of blood pressure during their college years are much more likely to have elevated pressures after a period of from five to ten years than those in whom the blood pressure was consistently normal while they were in college. Apparently also the probability of their having elevated blood

pressures in later years is in direct proportion to the frequency with which their pressures were elevated while in college.

Table 2 gives the systolic pressures of the several groups at the time of the follow-up study, and the chart shows the theoretical normal distribution curves which can be drawn from them. The actual distribution curves of these data are somewhat irregular and slightly skewed, but the theoretical curves are more easily followed and for comparative purposes are quite satisfactory. The differences in the pressures of the several groups at the time of the follow-up study are clearly shown by the areas of these curves above or below the various points on the millimeter scale. Each of the curves is significantly different from the others, and the percentage of overlapping between curves I and V is only 18.6 per cent.

TABLE 2.—Systolic Blood Pressures After from Five to Ten Years

Groups Based on Blood Pressures While in College	Total Number of Cases	Systolic Pressures on Follow-Up Study							
		100 to 119 Mm.		120 to 129 Mm.		130 to 139 Mm.		140 Mm. or More	
		Num-ber	Per-Cent	Num-ber	Per-Cent	Num-ber	Per-Cent	Num-ber	Per-Cent
I. Persistent hypertension...	15	0	0	3	20	4	27	8	53
II. Moderate elevation.....	16	2	12	6	37	6	37	2	12
III. Intermittent elevation....	24	2	8	13	54	7	29	2	8
IV. Transient elevation.....	45	15	33	17	37	11	25	2	5
V. Normal.....	55	36	70	17	31	2	4	0	0

In the terms of probability the results of this study would be stated as follows: (1) If a young man's systolic blood pressure in college is persistently above 140 mm., the chances are slightly more than 1 in 2 that it will be 140 mm. or more, and about 4 in 5 that it will be 130 mm. or more seven years later; (2) if his systolic pressure in college averages between 130 mm. and 140 mm., the chances are about 1 in 8 that it will be above 140 mm. and about 1 in 2 that it will be above 130 mm. seven years later; (3) if during the years at college his pressure is intermittently above 130 mm., the chances are 1 in 12 that it will be above 140 mm. and slightly more than 1 in 3 that it will be above 130 mm. seven years later; (4) if during his college years his systolic pressure is found to be above 130 mm. on only one occasion, there is about 1 chance in 20 that it will be above 140 mm. and about 1 in 4 that it will be above 130 mm. seven years later; and (5) if his systolic pressure during his college years is always under 130 mm., there is less than 1 chance in 100 that it will be above 140 mm. and only about 1 in 25 that it will be above 130 mm. seven years later.

## SUMMARY

1. A five to ten year follow-up study of systolic blood pressure in 155 young men is reported.

2. The average age of the young men at the time of the original examinations was 19.8 years, and at the time of the follow-up examination, 26.8 years.

3. The average systolic pressure of the group during the years at college was  $126.18 \pm 0.78$  mm. and at the time of the follow-up examination,  $123.97 \pm 0.57$  mm.

4. For purposes of comparison the group was divided on the basis of blood pressure records when in college into five subgroups as follows: (1) persistently elevated pressures; (2) moderately elevated pressures; (3) intermittently elevated pressures; (4) transiently elevated pressures, and (5) normal pressures.

5. At the time of the follow-up study the incidence of systolic pressures of 130 mm. or more in the several groups was as follows: group I, 80 per cent; group II, 50 per cent; group III, 37 per cent; group IV, 30 per cent, and group V, 4 per cent.

6. At the same time the incidence of systolic pressures of 140 mm. or more was as follows: group I, 53 per cent; group II, 12 per cent; group III, 8 per cent; group IV, 5 per cent, and group V, none.

7. At the time of the follow-up study only 2 persons showed blood pressures of over 160 mm., and both of these belonged to group I.

8. Although the number of cases in certain of the groups is small, the "chi square test" indicates that the possibilities of the differences between consecutive groups shown in table 2 being due to chance are as follows: between groups I and II, 8 in 100; between groups II and III, 42 in 100; between groups III and IV, 14 in 100, and between groups IV and V, 3 in 100.

9. These results apparently indicate that young men who show elevations of blood pressure, even though these are transient, are more likely to have high blood pressure after from five to ten years than men whose blood pressure at the earlier ages was consistently within so-called normal limits, and that the greater the degree or the frequency of the elevation in earlier years, the greater is the likelihood of high pressures later.

# HEREDITY IN HYPERTENSION

## A STATISTICAL STUDY

WILLIAM ALLAN, M.D.

CHARLOTTE, N. C.

From year to year the majority of those who discuss the causes of hypertensive cardiovascular disease list heredity as the chief, or at least a very important, factor.

This view is doubtless due to two clinical observations: In the first place, families in which a high percentage of the members in several generations have died from cardiovascular disease are frequently seen; but a generation ago the same was true of tuberculosis and led to the widespread idea that consumption was hereditary. In the second place, in the history of a majority of families, cardiovascular disease appears in each succeeding generation with noticeable frequency, owing, of course, to the high incidence of the disease in the general population. If the incidence of any hereditary trait is as high as 40 per cent, more than half the families in the general population will show the trait in both parents and children whether it be dominant or recessive. But this sort of evidence of heredity has the value merely of a "hunch."

O'Hare, Walker and Vickers<sup>1</sup> in Boston found a cardiovascular history twice as frequent among relatives of patients with hypertension as among relatives of controls, while Nuzum and Elliott<sup>2</sup> in California found the frequency of a cardiovascular history among relatives of patients with hypertension to be the same as among relatives of controls. Blanton<sup>3</sup> in Virginia found a family history of cardiovascular disease in 47 per cent of his patients with hypertension. As the ages and the relation of these relatives to the patients with hypertension and to the controls were not stated in any of these observations, such evidence is not competent. Weitz<sup>4</sup> obtained direct parental history of cardiovascular disease from 77 per cent of 82 patients with hypertension, and this evidence, so far as it goes, may be used to determine

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Read at the Forty-Eighth Annual Meeting of the Association of American Physicians, Washington, D. C., May 11, 1933.

1. O'Hare, J. P.; Walker, W. D., and Vickers, M. C.: Heredity in Hypertension, *J. A. M. A.* **83**:27 (July 5) 1924.

2. Nuzum, F. R., and Elliott, A. H.: An Analysis of 500 Cases of Arterial Hypertension, *Am. J. M. Sc.* **181**:630, 1931.

3. Blanton, W. B.: Study in Vascular Hypertension, *South. Med. & Surg.* **92**:495, 1930.

4. Weitz, W.: Etiology of Hypertension, *Ztschr. f. klin. Med.* **96**:151, 1923.

the inheritance of a unit trait, whether dominant or recessive. So far as I can find, this sums up the evidence for or against the heredity of hypertension.

For obvious reasons, in studying human heredity statistical methods must be used, and genetics, as based on Mendel's laws, being a mathematical science, definite percentages of parents, siblings and children of patients showing any unit trait will show the same trait. These percentages will depend on the incidence of the trait in the general population and on whether the trait is dominant or recessive. I have constructed tables<sup>5</sup> showing the expected incidence of any unit trait in parents, siblings and children of persons showing such trait, with incidences in the general population varying from 5 to 75 per cent. This gives something concrete to aim at, and in the study of any unit trait it remains for one to determine its incidence in the general population and to compare its frequency in parents, siblings and children with the percentages shown in the tables.

For the purpose of this study it is necessary to assume that hypertensive cardiovascular disease is inherited as a unit trait.

In considering hypertensive cardiovascular disease, the elevated blood pressure is merely the commonest and most easily measured symptom; so that only patients with hypertension have been used in this series. However, as clinical records of blood pressure date back only twenty years, other indications of hypertensive cardiovascular disease, such as apoplexy, sudden death from heart failure, and congestive heart failure, found in the histories have been given the same value as actual measurements of blood pressure in the patients.

A systolic pressure of 160 mm. of mercury or a diastolic pressure of 100 mm. has been used as the lower limit, indicating definite hypertension.

In trying to determine the frequency of hypertension in the general population, some fraction old enough to show the trait must be used. The actual finding of hypertension in persons more than 60 years of age should be the same as the potential presence of hypertension in those under 60, as modified by the following factors: First, some will have died of hypertension before the age of 60, but this positive evidence is not hard to get. Second, a few will have wasting diseases, such as cancer or tuberculosis, that obscure the trait. Third, some will not develop hypertension until after 60. Judging by clinical observation, the findings presented in this article are likely to be low rather than high.

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5. For construction of these tables see Allan, W.: The Inheritance of Migraine, *Arch. Int. Med.* **42**:590 (Oct.) 1928.



Such records of blood pressure as can be found at present in people over 60 years of age are derived chiefly from homes for the aged and from records of doctors and hospitals. These figures would naturally be somewhat too high. There are some figures obtained from insurance companies which, on the other hand, are likely to be somewhat too low. The New York Life Insurance Company, for instance, found that in 1931 heart diseases, apoplexy, nephritis and arterial diseases caused 32.5 per cent of the deaths of those insured by that company; in 1930, 47 per cent of the deaths of those above the age of 66 were due to these diseases. Table 1 shows the data easily available on the frequency of high blood pressure in persons more than 60 years old.

TABLE 1.—*High Blood Pressure in Patients More Than 60 Years Old*

Author	Age	Source	Blood Pressure	Number Examined	Number	Per Cent
Alvarez and Stanley: Arch. Int. Med. <b>46</b> : 17 (July) 1930	60+	Prisoners	160+	69	9	13
Willius: Am. J. M. Sc. <b>182</b> : 1, 1931	75-90	Mayo Clinic	160+	700	332	47
Davis: Human Biol. <b>2</b> : 264, 1930	75-83	Patients, J. H. H.	160+	50	21	42
Thompson and Todd: Lancet <b>2</b> : 503, 1922	75-92	Home for Aged, Eng.	160+	102	42	42
Allan: South. Med. & Surg. <b>92</b> : 491, 1930	61-95	Patients	160+	968	525	54
Wildt and Richter, quoted by Riseman and Weiss: Am. Heart J. <b>5</b> : 172, 1929	61-90	Patients	150+	409	183	45
Saller: Ztschr. f. d. ges. exper. Med. <b>58</b> : 683, 1928	60+	Outpatients	163+	510	194	38
Musser and Phillips, J. Lab. & Clin. Med. <b>15</b> : 633, 1930	70+	Outpatients	160+	50	21	42
Dublin, Fisk and Kopf: Am. J. M. Sc. <b>170</b> : 576, 1925	55+	Insured	152	1,094	252	23
				3,952	1,579	40

These figures indicate roughly that the incidence of hypertension in the general population is about 40 per cent.

My figures are based on findings in 485 patients with hypertension, 480 of whom gave direct parental history of hypertension, apoplexy, congestive heart failure or sudden death. This particular item is not a fair picture, since, in the absence of cardiovascular history, it is impossible to rule it out unless the parents live long enough and are actually examined.

Of the 480 patients one or both of whose parents had hypertension, there was a positive history for both parents in 131 instances, or 27 per cent, and for one parent in 349 instances, or 72 per cent. As may be seen in table 2, these figures are to be compared with expected frequencies of 32.4 per cent in both parents and 67.6 per cent in one parent in case the trait is dominant, and with 40 per cent in both parents

TABLE 2.—*Incidence of Unit Traits*

Incidence in General Popula- tion	Incidence of Any Unit Trait in Children When Present in						Incidence of Any Unit Trait When Present in Children in						Incidence of Any Unit Trait in Siblings of Those					
	Both Parents		One Parent		Neither Parent		One or Both Parents		Both Parents		One Parent		Neither Parent		With Trait		Without Trait	
	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R
5%	75.60	100	50.60	18.28	0	3.34	100	39.73	5.00	5	96.14	34.73	0	60.31	52.08	37.44	2.41	4.08
10%	76.28	100	51.30	24.00	0	5.76	100	53.25	7.62	10	92.34	43.25	0	46.76	54.36	43.34	5.07	6.30
15%	76.96	100	52.00	27.91	0	7.79	100	62.45	11.49	15	88.40	47.45	0	37.52	56.55	48.10	7.66	9.15
20%	77.70	100	52.78	30.90	0	9.55	100	69.45	15.51	20	83.86	49.45	0	30.56	58.29	52.36	10.27	11.91
25%	78.47	100	53.00	33.33	0	11.09	100	75.00	19.61	25	80.04	50.00	0	25.00	60.73	56.25	12.90	14.58
30%	79.24	100	54.45	35.40	0	12.53	100	79.55	23.77	30	76.23	49.55	0	20.45	63.45	59.89	15.67	17.19
35%	80.08	100	55.37	37.20	0	13.84	100	83.35	28.03	35	71.98	48.35	0	16.70	64.35	63.35	18.44	19.76
40%	80.97	100	56.37	38.75	0	15.01	100	86.50	32.39	40	67.65	46.50	0	13.51	68.15	66.61	21.25	22.25
45%	81.84	100	57.38	40.15	0	16.12	100	89.17	36.83	45	63.12	44.17	0	10.72	69.50	70.23	24.19	24.72
50%	82.84	100	58.58	41.42	0	17.15	100	91.42	41.42	50	58.58	41.42	0	8.53	72.86	72.85	27.14	27.14
55%	83.88	100	59.85	42.61	0	18.16	100	93.35	47.92	55	53.85	38.35	0	6.68	75.27	75.84	30.21	29.56
60%	84.99	100	61.25	43.62	0	19.03	100	94.90	51.00	60	49.00	34.90	0	5.00	77.80	78.72	33.38	31.88
65%	86.16	100	62.80	44.63	0	19.92	100	96.23	56.00	65	43.96	31.24	0	3.76	80.21	81.55	36.70	34.23
70%	87.47	100	64.60	45.55	0	20.75	100	97.33	61.15	70	38.76	27.33	0	2.68	82.80	84.33	40.12	36.56
75%	88.92	100	66.67	46.40	0	21.52	100	98.20	66.67	75	33.33	23.20	0	1.80	85.65	87.05	43.35	40.83
	70.6%		68.4%				99%		27%		72%			1%	60%			
Author's data	359+		469+				480+		131 both positive						501+			
	92—		216—				5—		349 one positive						333—			
	311 ?		500 ?				406 ?		5 both negative						843 ?			
	762		1,185				951		485						1,677			

and 46.5 per cent in one parent in case the trait is recessive. The early death of one parent in many instances would tend to increase the finding of hypertension in one parent instead of in both.

In 337 families in which the number of children was ascertained, there were 1,923 children, an average of 5.7 children or 4.7 siblings per family.

In 121 of the 337 families there was positive history of hypertension in both parents; of the 762 children in this group, 359 had hypertension, 92 did not, and 311 were too young or information concerning this fact was not obtained, giving a positive finding of 79.6 per cent. This is to be compared with 81 per cent in case of a dominant trait and 100 per cent in case of a recessive trait. In the other 216 families, there was a history of hypertension in one parent; of the 1,185 children in this group, 469 had hypertension, 216 did not, and 500 were too young or this information was not obtained, giving a positive finding of 68.4 per cent, as compared with an expected dominant frequency of 56 per cent and recessive frequency of 38.7 per cent. As yet, I have no control group of the children of normal persons large enough to tabulate.

In 349 families with 1,677 siblings of patients with hypertension, 501 had hypertension, 333 did not, and 843 were too young or this information was not obtained, giving a positive finding of 60 per cent in the siblings of these patients. As the expected frequency here is 68 per cent for a dominant trait and 66.6 per cent for a recessive trait, the study of siblings is not useful in differentiating between dominance and recessiveness, but tends to indicate the hereditary nature of hypertension. My data on the siblings of normal persons are not sufficient to tabulate.

The figures I have submitted suggest the possibility that hypertensive cardiovascular disease may prove to be a dominant unit trait, but they are much too few to warrant any definite conclusions. At the present time, therefore, the many statements in the literature that hypertension is either partly or wholly hereditary are without justification. This question can be answered only after many more facts have been gathered and analyzed from a genetic standpoint.

# POLYTROPOUS ENTERONITIS (ACUTE INFECTIOUS GASTRO-ENTERITIS, SPENCER'S DISEASE)

IS IT A FORM OF INFLUENZA?

H. A. WILDMAN, M.D.

IMLAY CITY, MICH.

Although influenza may be complicated by disturbances of the gastro-intestinal tract, many able clinicians have felt for some time that there is no true gastro-intestinal form of influenza in which the primary infection invades the alimentary canal. Boone<sup>1</sup> described a clinical condition with abdominal symptoms, which is usually called intestinal influenza, perhaps for want of a better name. Zahorsky,<sup>2</sup> McLean<sup>3</sup> and Lucas<sup>4</sup> described what is probably the same condition in children. Spencer<sup>5</sup> studied similar cases in the national parks of the West during the summers of 1929 and 1930. He stated that the disorder is a summer disease; on the other hand, Zahorsky said that the cases studied by him occurred in winter, and he accordingly gave the disease the name hyperemesis hiemis (winter vomiting disease).

The present report is based on a study of a group of about 750 college students seen between September, 1927, and June, 1932, who presented the same type of clinical picture, namely, sudden, acute onset of one or more of the following symptoms: nausea, vomiting, diarrhea, dull headache, abdominal distress. I believe that these cases and those described by Boone, Zahorsky, McLean, Lucas and Spencer are cases

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From the Department of Hygiene, College of Wooster.

The following assistance was given: statistical studies by Miss Miriam Winkler, my secretary; classification of isolated organisms by Dr. G. W. McCoy, Director of the National Institute of Health, Washington, D. C.; Dr. E. O. Jordan, Chairman of the Department of Bacteriology, the University of Chicago, and Dr. W. W. Ford, Professor of Bacteriology, Johns Hopkins University. Some epidemiological material was furnished by Dr. R. R. Spencer of the United States Public Health Service. Some of the drugs for the research were supplied by Sharp & Dohme, Baltimore, and by the William S. Merrel Company, Cincinnati.

1. Boone, F. H.: Gastro-Intestinal Grippe (So-Called), *Canad. M. A. J.* **19**:63, 1928.

2. Zahorsky, John: Hyperemesis Hiemis or Winter Vomiting Disease, *Arch. Pediat.* **46**:391, 1929.

3. McLean, C. C.: Seasonal Gastro-Enteritis, *South. M. J.* **24**:624, 1931.

4. Lucas, R. T.: Epidemic Vomiting or Intestinal Influenza, *New Orleans M. & S. J.* **83**:213, 1930.

5. Spencer, R. R.: Unusually Mild Recurring Epidemic Simulating Food Infection, *Pub. Health Rep.* **45**:2867, 1930.

of the same condition or very closely related conditions. The protean nature of this disorder, in which the symptoms are predominantly gastro-intestinal, makes fitting the proposed name "polytropic enteronitis" (polytropos-changeful, complicated; enteron-alimentary canal).<sup>6</sup> Because of Spencer's illuminating report and because he thought that the malady was a distinct disease, I shall also refer to it as Spencer's disease.

The findings here presented merely suggest an entity distinct from influenza, food poisoning and conditions with similar symptoms. Much more extensive investigation is needed to establish its identity firmly. Ordinary laboratory animals are not susceptible to the disorder. Human experimentation has been inexpedient. At the first opportunity I plan to use one of the simians. I have wondered if Jo Mendi, the trained chimpanzee at the Detroit zoo, was infected by human beings with polytropic enteronitis when he was so ill last year. The condition was called paradysentery.

#### ETIOLOGY

I have seen cases of polytropic enteronitis in persons ranging in age from 1 day to the late decades of life. My experience with the disease suggests that older children and young adults are more susceptible. Males and females are equally affected. I have known epidemics and sporadic cases of the disorder to occur at all times during the year. Personal observation in different localities, surveys and reports furnished by Dr. Spencer indicate that it is widely distributed and that climate has no influence. No predisposing factors have been determined. The responsible organism is unknown, but it is apparently spread by secretions from the nose and throat, as is illustrated by the following instance:

L. B. was admitted to the hospital on May 22, 1930, because of nausea and a chilly feeling. The previous day she felt chilly and had malaise, a "light-headed" feeling and an intermittent headache. A diagnosis of polytropic enteronitis complicated by malaria was made. About 6 p. m. on May 23 she was visited by her brother, M. B., who took a sip of water from her drinking glass. At midnight on May 24 (thirty hours later) M. B. was suddenly seized with shifting abdominal cramps and diarrhea. The diagnosis was polytropic enteronitis. M. B. had been in the hospital under observation for a wholly unrelated condition since May 20. None of the hospital staff who ate the same food was ill. There were no other cases in the hospital and no contact with known cases other than that of L. B.

Atypical colon bacilli, atypical Flexner bacilli and atypical organisms belonging to the genus *Salmonella* were found in the stools of the

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6. Suggested by Miss Eva May Newman, Assistant Professor of Greek, College of Wooster.

patients whom I was treating for this condition. McBroom<sup>7</sup> found atypical organisms of this group in a series of patients with various gastro-intestinal disorders. Therefore the presence of such organisms may be a coincidence. Fothergill<sup>8</sup> found slow lactose-fermenting gram-negative bacilli in the stools of infants with diarrhea. Some research workers have suspected such organisms of being more virulent than the ordinary organisms of the colon group. Most of the atypical organisms found presented some characteristics resembling the colon bacillus, even the atypical Flexner bacilli. Since I could produce no agglutinating serums with vaccines sterilized by heat or formaldehyde or with young living cultures, I was unable to determine the relationships serologically.

Cultures of any organisms taken from the throats of patients, when fed to mice, produced slowing of lactose fermentation by colon bacilli taken from their rectums. Attempts to isolate a symbiotic filtrable virus capable of producing such a change in colon bacilli were unsuccessful. Electrophoretic studies<sup>9</sup> of these organisms were not carried far enough to yield any suggestive data. As matters stand, I do not know whether these organisms are present as the cause or as the result of the disease, or whether they are merely coincidental. They could not be isolated from cultures taken from the throats of patients.

Attempts to isolate the organisms described by Rockwell,<sup>10</sup> Rosenow,<sup>11</sup> Fellman,<sup>12</sup> Harrington<sup>13</sup> and Hinkelmann<sup>14</sup> were unsuccessful. I believe that, with the exception of Rockwell, these investigators were dealing with a clinical entity other than polytropic enteronitis, in view of the fact that the conditions which they described were more serious and more persistent and were at times fatal. None of the patients in the group studied by me died or appeared to be dangerously ill.

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7. McBroom, Josephine: Paratyphoid, Proteus and Related Organisms in Health and in Miscellaneous Intestinal Disorders of Man, *J. Prev. Med.* **4**:239, 1930.

8. Fothergill, L. D.: Unusual Types of Non-Lactose Fermenting Gram-Negative Bacilli from Acute Diarrhea of Infants, *J. Infect. Dis.* **45**:393, 1929.

9. Lieb, C. W., and Chapman, G. H.: Studies in Intestinal Intoxication, *New York State J. Med.* **29**:1323, 1929.

10. Rockwell, G. E.: Report of Five Cases of Intestinal Grippe, with Bacteriologic Findings, *J. Med.* **8**:82, 1927.

11. Rosenow, E. C.: Experiments in Etiology of Gastro-Intestinal Influenza, *J. Infect. Dis.* **26**:557, 1920.

12. Fellman, G. H.: Report of Epidemic of Gastro-Enteritis, *Wisconsin M. J.* **20**:227, 1921.

13. Harrington, A. H.: Acute Infectious Enteritis with Polyneuritic Symptoms, *Bull. State Board of Health of Rhode Island* **3**:17, 1917.

14. Hinkelmann, A. G.: Bacteriology of So-Called Gastro-Intestinal Influenza, *Illinois M. J.* **28**:353, 1915.

Although I have been successful in isolating pleomorphic organisms from the blood and saliva of patients with influenza by using Kendall's<sup>15</sup> technic, cultures made from filtrates of the stool and saliva and cultures made from the blood of patients with polytropic enteronitis were sterile. If the organisms described by Kendall and by Olitsky and Gates<sup>16</sup> are the cause of influenza, it seems that one should be able to find them as frequently in patients with polytropic enteronitis as in those with influenza, if the two conditions are forms of the same disease.

In an epidemic among the students of the College of Wooster in November, 1927, *Bacillus pyocyaneus* was isolated in large numbers from the milk used in the women's dining rooms. The explosive nature of the epidemic suggested food poisoning, but the organisms in the milk were all that could be found that was suggestive of the source of trouble. Epidemiologically and clinically, the outbreak was wholly unlike the one described by Cooley.<sup>17</sup> The fact that I was dealing with college students instead of infants may account for some of the differences noted. There is a question whether the epidemic was caused by poisoning with the products of *B. pyocyaneus* or by polytropic enteronitis. *B. pyocyaneus* has not been found in the milk since that time. A colony of atypical proteus bacilli<sup>18</sup> was found in a culture from one sample of milk, and on another occasion an organism resembling a staphylococcus<sup>19</sup> was found, which failed to grow on subcultures from the original blood agar plates.

The feeding of isolated atypical organisms failed to produce symptoms in rats and mice. Atypical Flexner bacilli affected the animals only when given intraperitoneally. When they were so given in small doses the animal showed few if any signs of illness and rapidly destroyed the organisms. Serial passage through animals failed to

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15. Kendall, A. I.: A Filterable Organism from Influenza, *Science* **74**:129, 1931.

16. Olitsky, P. K., and Gates, F. L.: Experimental Studies of Nasopharyngeal Secretions from Influenza Patients, *J. A. M. A.* **74**:1497 (May 29) 1920.

17. Cooley, T. B.: An Epidemic of Infantile Diarrhea Apparently Caused by *Bacillus Pyocyaneus*, *J. A. M. A.* **50**:607 (Feb. 22) 1908.

18. Bengston, I. A.: Proteus Group of Organisms with Special Reference to Reactions of Agglutination and Fermentation and Classification, *J. Infect. Dis.* **24**: 428, 1919.

19. (a) Jordan, E. O.: Production by Staphylococci of Substances Causing Food Poisoning, *J. A. M. A.* **94**:1648 (May 24) 1930; Staphylococcus Food Poisoning, *ibid.* **97**:1704 (Dec. 5) 1931. (b) Jordan, E. O., and Hall, J. B.: Case of Food Poisoning Apparently Due to Staphylococcus, *J. Prev. Med.* **5**:387, 1931. (c) Dack, G. M.; Cary, W. E.; Woolpert, O., and Wiggers, H.: Outbreak of Food Poisoning Proved to Be Due to Yellow Hemolytic Staphylococcus, *ibid.* **4**: 167, 1930.

increase the virulence of the organisms. When sufficient doses were given the animals usually died within about twelve hours, apparently from toxemia.

#### EPIDEMIOLOGY

As I have indicated, the relation of Spencer's disease to influenza is doubtful, but epidemics of a condition like Spencer's disease have been reported in close association with epidemics of influenza since the World War. This is probably a coincidence. As is shown by the accompanying chart, only once in five years did epidemics of the two disorders occur simultaneously in the group studied (January, 1930). I noticed a marked increase in the number and virulence of cases a few weeks after the marked epidemic of influenza in February and March, 1932.

Although differential diagnosis is difficult at times, the two disorders are as a rule clinically different. Table 1 shows that polytropic enteronitis and influenza do not confer immunity against one another. It will also be noted that influenza confers immunity lasting at least two months to subsequent attacks of the same disorder. Vaughan and Jordan (quoted by Rosenau<sup>20a</sup>) believed that immunity in influenza probably does not last more than seven months. In polytropic enteronitis, however, the immunity is apparently of much shorter duration than in influenza, as is indicated in table 1. Recurrent attacks occur at intervals of from one to six weeks. One patient reported eleven successive attacks in about as many weeks. Fortunately, this is unusual.

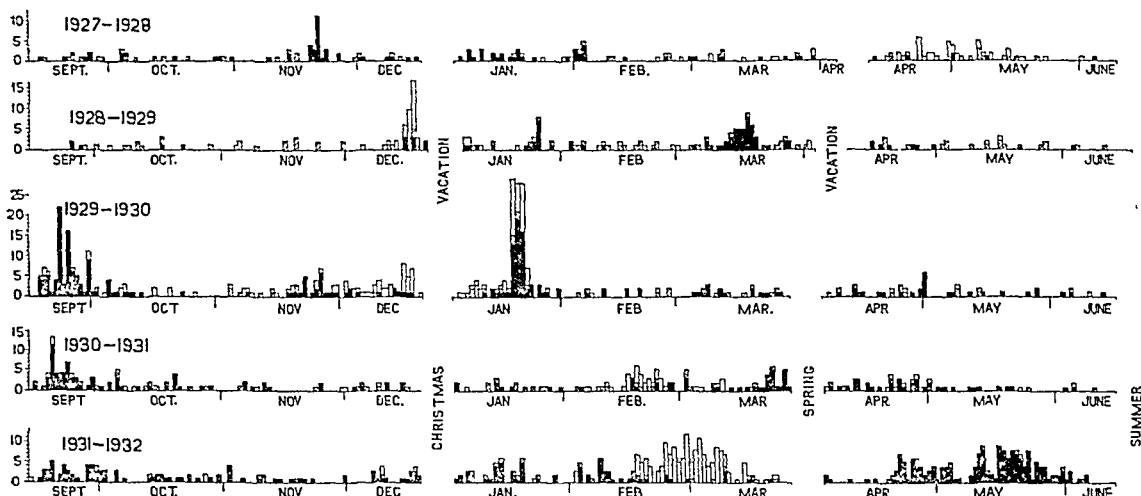
Food and water are apparently not vectors, although they may be transient fomites. The condition is not food poisoning. The organisms of typical food poisoning were absent in patients and in suspected food. There were no common food factors. The sources of food, milk and water varied widely. Laboratory animals which are ordinarily susceptible to food poisoning could not be infected with the infective material taken from patients. Cases developed within from twenty-four to forty-eight hours following contact with a known case, and epidemics usually reached their peak within from three to five days instead of from one and one-half to twelve hours after the eating of a suspected meal, as would be the case with food poisoning. The incubation period in food poisoning may be as long as thirty hours, but the epidemic peak is reached within a few hours.

The city and campus water supplies are independent, and some students commuting daily from surrounding rural areas rarely, if ever,

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20. Rosenau, M. J.: (a) *Preventive Medicine and Hygiene*, ed. 5, New York, D. Appleton and Company, 1927, p. 245; (b) *Some Fallacies in Diagnosis of "Ptomain Poisoning,"* *M. Clin. North America* 2:1541 (March) 1919; (c) *Experimental Lunch with Canned Food Containing Bacteria*, *ibid.* 3:913 (Jan.) 1920.





Relation of polytypous enteronitis to influenza, as shown by the incidence of cases. The black columns indicate polytypous enteronitis; the white columns, influenza, and the white columns with diagonal lines, undiagnosed condition with symptoms similar to those of polytypous enteronitis.

TABLE 1.—*Immunity Reactions in Polytypous Enteronitis and in Influenza \**

Polytypous Enteronitis		Influenza		Polytypous Enteronitis and Influenza	
Case	Date of Attack	Case	Date of Attack	Case	Date of Attack
20 E.....	3/11/29 3/18/29	86 B.....	(10/ 4/28) (12/15/28)	181 F.....	1/20/32 (2/26/32) 5/12/32
128 F.....	1/ 4/32 1/20/32	245 D.....	(3/29/28) (2/15/31) (4/27/31)	19 B.....	4/12/28 (4/15/28)
291 G.....	11/ 8/30 3/25/31 1/28/32 2/25/32 3/ 7/32 5/14/32 5/27/32† 6/ 6/32	121 H.....	(12/17/31) ( 3/ 7/32)	291 G.....	2/25/32 (2/29/32) 3/ 7/32
23 H.....	3/27/32 4/ 3/32	212 D.....	(2/23/28) (5/ 7/28)	143 B.....	1/18/29 (1/21/29)
44 G.....	2/27/31 3/17/31 3/27/31	213 H.....	(2/27/32) (4/26/32)	71 F.....	1/ 7/32 (2/11/32) 5/25/32
43 D.....	11/21/29 12/14/29 1/21/30 9/22/30 2/20/31 3/23/31			96 C.....	(12/18/28) 1/15/29
				131 F.....	2/11/30 (2/17/30)
				124 G.....	(2/24/31) 3/22/31

\* Cases of influenza are enclosed in parentheses; other cases are those of polytypous enteronitis. It should be noted that recurrent attacks of polytypous enteronitis occurred at intervals of a week or more, whereas no two attacks of influenza were less than eight weeks apart. Furthermore, attacks of typical influenza followed attacks of polytypous enteronitis in as short a time as three days. Patient 291 G had typical polytypous enteronitis four days following the onset of mild respiratory influenza from which she was convalescing when the attack occurred.

† Reported eleven recurrent attacks since Feb. 1, 1932.

drink water on the campus. The campus water comes from deep wells and shows only an occasional air contaminator on bacteriologic examination. The city water, which comes from a 40 foot (12 meter) well in a valley, is examined on the average every two weeks; it has shown *Bacillus coli* only twice in six years and then only when there were bad floods. The milk is of exceptional quality from a bacteriologic standpoint.

Animals are apparently not vectors. The college kitchens are kept unusually free from rodents and flies. A third of the students or less board off the campus.

Since I had patients in whom the mode and time of contact with other cases were known with certainty, I feel amply justified in drawing the conclusion that the infection is spread by secretions from the nose and throat. The epidemiologic characteristics point to the same source of infection. Room-mates may transmit the disease to one another, and in the dining halls several students at one table may have the condition, while those at other tables may be free. I have not been able to settle the question of healthy carriers.

#### PATHOGENESIS

Although the organisms seem to be in the nose and throat, only about 10 per cent of the patients complained of respiratory symptoms. Aching and tenderness over the frontal sinuses suggested irritation and toxic absorption from their mucous membranes, but the clearness revealed by transillumination and the appearance of the visible parts of the respiratory mucous membranes indicated that there was little congestion except in patients with definite respiratory symptoms. The infrequency of leukocytes in the stools suggested that a similar condition obtained in the alimentary canal, a point which might be partly settled by gastroscopy and sigmoidoscopy.

Unfortunately, vomitus was not carefully examined. There were no red cells in the stools, but I did not make tests for occult blood which might account for the darker stools in some cases. In one epidemic a patient with atypical acute appendicitis had a large, swollen, spindle-shaped appendix, with three large hemorrhagic areas under the serosa. Phillip Potter<sup>21</sup> of Bellevue Hospital noted in a patient with a similar condition petechial hemorrhages under the serosa of the terminal part of the ileum and under that of the cecum and appendix, with red lymph nodes in the region. St. John<sup>21</sup> of the New York Presbyterian Hospital noted cherry red abdominal lymph nodes in another patient. In the typhlo-appendical type of Spencer's disease there is usually tenderness over the region of the terminal part of the ileum and over the

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21. Personal communication.

cecum and appendix. A child, aged 6, whom I saw in Detroit in May, 1926, had abdominal lymphadenitis; a normal appendix was removed at operation. This may have been a case of the typhlo-appendical type of Spencer's disease. F. F. Russell, director of the International Board of Health, told me of the finding of exudative peritonitis in a patient on whom an operation was performed during an epidemic in the Canal Zone. Two other patients with similar conditions recovered without an operation. Whether secondary invaders play a part in the production of such pathologic conditions I cannot say. Some of the atypical organisms found in the stools were hemolytic.

Fairbanks<sup>22</sup> discussed the neurologic aspects of food poisoning. In polytropic enteronitis there is much evidence of imbalance of the autonomic nervous system, with the effect of the vagus predominating. Peripheral neuritis is common, and there may be myositis, particularly of the abdominal wall. There is tenderness over portions of the spine, particularly over the three upper dorsal vertebrae. These rheumatoid symptoms suggest a toxic or metastatic disorder. Whether it is due to the primary infection or to the secondary invaders is not clear. Vasomotor instability, largely in the abdominal viscera, may result partly from autonomic imbalance and partly from local toxic vasodilatation.

The fact that a considerable number of patients have recurrent attacks after a six day interval suggests that the disease may have a phasic nature. One woman student reported eleven recurrent attacks in about as many weeks, causing me to wonder if the condition might be an allergic phenomenon. One attack occurred on the second day after the fever had gone down following an attack of mild respiratory influenza. I could not account for the attacks on the basis of any other gastro-intestinal condition than Spencer's disease. Only one patient, a woman with a chronic disorder of the bowels which was diagnosed as irritable colon, was tested for allergic phenomena according to the method of Dorst and Morris.<sup>23</sup> She was apparently sensitive to *Bacillus cloacae* taken from the stool during an attack of polytropic enteronitis, but the preparation of vaccine for the test could not be completed until several days after the attack had subsided. The chronic condition was apparently temporarily improved after the reaction to the sensitization test had subsided.

#### SYMPTOMS

Clinically, polytropic enteronitis, or Spencer's disease, is characterized by an acute, sudden onset of one or more of the following symp-

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22. Fairbanks, A. W.: *Neurologic Aspects of Food Poisoning*, Boston M. & S. J. **176**:413, 1917.

23. Dorst, S. E., and Morris, R. S.: *Bacterial Hypersensitivity of Intestinal Tract*, Am. J. M. Sc. **180**:650, 1930.

toms named in the approximate order of their frequency: anorexia or nausea, vomiting, diarrhea, dizziness on standing, dull headache which is usually frontal, aching in the back and legs or generalized aching, abdominal distress or cramps, chilliness or alternate sensations of heat and cold, cold in the head, sore throat, constipation. Retching is rare; tenesmus is unusual, and blood has never been noted in the stools grossly or microscopically. Vomiting may be almost projectile at times. The usual incubation period is from thirty to thirty-six hours.

#### PHYSICAL FINDINGS

Physical examination frequently shows nothing significant. The patient may not appear markedly ill unless he is vomiting, although children may have an ashy look, sunken eyes, a listless expression and an acetone breath. The skin is usually dry or flushed; it is rarely cool and moist, with some pallor, and in children it is dehydrated. Red dermographia is present. The temperature is frequently subnormal; fever is slight and transient as a rule, but may rise to 104 F. in severe cases; a relatively slower pulse at the febrile fastigium is common.

There is usually tenderness over portions of the colon, especially over the sigmoid flexure. Sometimes there is tenderness over McBurney's point and the epigastrium. The abdominal wall may be tender, particularly over the rectus abdominis muscles. The spleen appeared to be transiently enlarged in one patient, a boy 5 years old. There may be tenderness over some of the vertebrae, especially over the first three dorsal segments, and also along the trunks of the spinal nerves and their areas of distribution.

When there are respiratory symptoms, the nose and throat may exhibit a slight redness or injection, sometimes swelling, and rarely discharge. These symptoms and findings may be a coincidence, but they precede the development of other symptoms by an interval of about two days so often as to suggest a definite relationship to the disease in some cases. In spite of tenderness over the frontal sinuses, the latter are as clear to transillumination as usual. There are marked dizziness and a sudden rise and fall of blood pressure on standing, resulting in a fall of pulse pressure.

#### LABORATORY FINDINGS

The blood may show polymorphonuclear leukocytosis, with as many as 15,000 cells per cubic millimeter, which is often followed by secondary leukopenia about twenty hours later (table 2). The stools are frequently offensive in odor; they are sometimes darker than normal, and, in early diarrhea, are watery, with fine flecks of mucus but with no pus or blood cells. Undigested particles of food are rarely present. Mucus

is abundant later. Atypical organisms of the colon group apparently persist for about from ten days to two weeks after the attack.

#### COURSE AND TYPES

Acute symptoms often last only from eighteen to twenty-four hours and are followed by rapid recovery from the residual weakness. Diarrhea may last two weeks in some epidemics; in some cases it may last as long as three weeks. Dizziness on standing lasted as long as six weeks in one patient and four weeks in another.

For convenience of study I have divided cases of this disorder into six types, listed in the relative order of their frequency, with their predominant symptoms:

- Type 1. Gastro-enteric: nausea, vomiting, diarrhea
- Type 2. Enterocolic: diarrhea, sometimes cramps
- Type 3. Gastric: anorexia, nausea, vomiting
- Type 4. Neurocirculatory: dizziness, dull headache
- Type 5. Typhlo-appendical: like acute appendicitis except for diarrhea, dizziness on standing and dull headache; fever less constant; less marked and less sharply localized tenderness in lower part of right quadrant; less rigidity of abdominal wall
- Type 6: Colic: Cramps or severe midabdominal pain, usually with constipation

#### COMPLICATIONS AND PROGNOSIS

Unless respiratory symptoms are considered as complications, the latter were rare in my series. In two or three instances subacute exacerbation of chronic appendicitis apparently complicated a case of the typhlo-appendical type of Spencer's disease. A flare-up in a malarial infection, caused by polytropic enteronitis, made differential diagnosis difficult in one case.

Although a large number of the patients were very ill, there were no deaths due to this condition and, so far as I know, no sequelae. I have known about a third of the student body of the college to be ill during an epidemic, most of them within one week. From three to five distinct epidemics occurred each year, and large numbers of sporadic cases occurred throughout the year. The morbidity rate was amazing; some patients remained in bed and were severely ill for three or four days at a time, and many others were partially incapacitated for as long as two weeks or longer.

#### DIFFERENTIAL DIAGNOSIS

There is a great variety of conditions which must be differentiated from polytropic enteronitis. Some of these, in which differentiation is extremely important, will be mentioned. Vigilance in regard to food

poisoning<sup>24</sup> must never relax. So far as I know, no one has ever died from Spencer's disease, but food poisoning has a significant mortality rate. Therefore, one must promptly detect and remove the source of food poisoning as well as find and treat efficiently all persons suspected of having it. The same statements apply to typhoid and to bacillary<sup>25</sup> and amebic dysentery, which may at times be difficult to differentiate. Some fishes and mushrooms, potatoes grown or stored under certain conditions,<sup>22</sup> the leafy portions of rhubarb, saltpeter used for the preservation of meat<sup>20b</sup> and foods contaminated by staphylococci,<sup>19</sup> streptococci,<sup>20</sup> *B. enteritidis*,<sup>27</sup> *B. paratyphosus* A and B,<sup>28</sup> *B. suipestifer* (*aertrycke*)<sup>29</sup> and, possibly, *B. proteus*,<sup>30</sup> *B. cloacae*,<sup>31</sup> *B. coli* and *B. subtilis*<sup>32</sup> may be responsible for a clinical picture which can be differentiated from polytropic enteronitis only with difficulty. Botulism<sup>32</sup> is so distinctive that it offers no difficulty in regard to diagnosis, unless it is complicated by other types of food poisoning or by other conditions.

Water containing increased amounts of organic matter has been blamed for epidemics similar to those of polytropic enteronitis in some cities of the Ohio River valley.<sup>33</sup> I doubt that commercial canned goods ever produce food poisoning, unless they are obviously spoiled.<sup>20c</sup>

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24. (a) Jordan, E. O.: Food Poisoning and Food-Borne Infection, ed. 2, Chicago, University of Chicago Press, 1930. (b) Geiger, J. C.: Poisoning by Food Probably Due to Contamination with Certain Bacteria; Epidemiologic Analysis of Seven Hundred and Forty-Nine Reported Outbreaks in the United States, *J. A. M. A.* **81**:1275 (Oct. 13) 1923. (c) Rosenau, M. J., and Weiss, Harry: Food Infections with an Illustrative Outbreak, *J. A. M. A.* **77**:1948 (Dec. 17) 1921.

25. Warren, S. H.: Outbreak of Illness Caused by *B. Dysenteriae* Flexner, *Lancet* **2**:494, 1927.

26. Cary, W. E.; Dack, G. M., and Myers, E.: Institutional Outbreak of Food Poisoning Possibly Due to *Streptococcus*, *Proc. Soc. Exper. Biol. & Med.* **29**:214, 1931.

27. Fairbanks.<sup>22</sup> Rosenau and Weiss.<sup>24c</sup>

28. Bernstein, H. S., and Fish, E. S.: Food Poisoning by the *Bacillus Paratyphosus* B, *J. A. M. A.* **66**:167 (Jan. 15) 1916. Geiger, J. C., and Jordan, E. O.: Two Outbreaks of Food Poisoning Apparently Due to Bacilli of Paratyphoid Enteritidis Group, *J. Infect. Dis.* **32**:471, 1923. Fairbanks.<sup>22</sup> Rosenau and Weiss.<sup>24c</sup>

29. Gill, D.: Fatal Food Poisoning Due to *Bacillus Suipestifer*, *Brit. M. J.* **2**:857, 1924. McWeeney, E. J.: Gastro-Enteritis Due to *Bacillus Aertrycke*, *Brit. M. J.* **2**:451, 1916.

30. Bengston.<sup>18</sup> Fairbanks.<sup>22</sup> Jordan,<sup>24a</sup> p. 141.

31. Buchanan, E. B., and Megrail, E.: Two Outbreaks of Food Poisoning Probably Due to *B. Cloacae*, *J. Infect. Dis.* **44**:235, 1929.

32. Burke, Victor, and May, C. W.: Presumptive Test for Etiologic Factor in Bacterial Food Poisoning, *J. A. M. A.* **79**:1669 (Nov. 11) 1922. Fairbanks.<sup>22</sup>

33. Veldee, M. V.: An Epidemiologic Study of Suspected Water-Borne Gastro-Enteritis, *Am. J. Pub. Health* **21**:1227, 1931.

The typhlo-appendical type of polytropic enteronitis may simulate acute appendicitis closely or may even stir up an old chronic appendical infection. If there is doubt, it is better to remove a normal appendix than to risk a fatal issue from pyogenic appendicitis. I have had several patients with subacute exacerbation of chronic appendicitis which subsided without operative intervention within one or two weeks after a flare-up caused by polytropic enteronitis.

The colic type frequently resembles other acute abdominal conditions. In this type codeine and enemas are used freely, but they may lead to disastrous results in mesenteric thrombosis, volvulus, intussusception or strangulation of the bowel. A "lightheaded" or dizzy feeling on standing and dull aching over the frontal sinuses are two of the most characteristic symptoms of polytropic enteronitis, but they should not be accepted as absolutely pathognomonic.

Error in diagnosing some conditions, e. g., catarrhal jaundice and influenza with gastro-intestinal symptoms, is not serious, but may delay recovery through lack of proper treatment. In catarrhal jaundice, abdominal distress is high (epigastric), and there is often tenderness over the liver. Light-colored stools, bloating, eructations and malaise are the rule even before the jaundice is evident. Transduodenal stimulation with a 25 per cent solution of magnesium sulphate, hot olive oil and hot saline drip are in order, measures which are entirely out of place in Spencer's disease. In influenza the abdominal symptoms usually appear later than in Spencer's disease; the weakness and depression are more marked, and the leukopenia is primary instead of secondary, with leukocytosis occurring later in some instances. Convalescence is slower, and the patient requires more prolonged nursing to avoid complications and sequelae.

Burgess<sup>34</sup> described influenza complicated by jaundice. The appearance of gastro-intestinal symptoms at a later time than in Spencer's disease is noteworthy. Abels<sup>35</sup> also described cases in which there were gastro-intestinal symptoms. The early appearance of gastro-intestinal symptoms in a case described by Blake<sup>36</sup> raises a question as to the accuracy of the diagnosis of influenza. Leukopenia was noted several days after the onset, which would be consistent with polytropic enteronitis.

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34. Burgess, A. M.: *Influenzal Gastro-Duodenitis with Jaundice*, Rhode Island M. J. **6**:166, 1923.

35. Abels, H.: *Das selbständige Magen-Darmbild der Grippe*, Wien. klin. Wchnschr. **41**:1482, 1928.

36. Blake, G.: "Intestinal Influenza," M. Clin. North America **8**:1545 (March) 1925.

Migraine, gastric crises and many other conditions in which gastrointestinal symptoms occur must also be kept in mind in making the differential diagnosis.

#### REPORT OF CASES

*Gastro-Enteric Type.*—A girl, aged 19, on Dec. 10, 1931, felt tired and complained of aching back of the eyes and in the temples; her throat was "rough"; she had had a nasal discharge for a week. She could not sleep because of epigastric heaviness and fulness. About midnight there was nausea, with a dull epigastric ache. She vomited at 4 a. m. and felt dizzy and faint on rising. That morning there were stiffness and a tired feeling between the shoulders; the legs were tired; she vomited several times. She passed a slightly constipated stool at 8:30 a. m. and took a cathartic at noon. She was admitted to the hospital at 1 p. m. with a temperature of 98.6 F. and a pulse rate of 108. She appeared somewhat ill; the skin was warm and dry; the nose was slightly red and moist. The sinuses were clear, and examination of the throat showed nothing significant; the posterior cervical lymph nodes were slightly enlarged but were not tender. Examination of the abdomen gave negative findings. There was slight tenderness over the following vertebrae: the first cervical, the first four dorsal and the fourth and fifth lumbar. Atropine sulphate in a dose of 0.0012 Gm. was given intramuscularly at 3:15 p. m. The temperature was 100 F. and the pulse rate was 112 at 4 p. m. The white blood count at 3:30 p. m. was 14,500 per cubic millimeter, with 88 per cent polymorphonuclears, 8 per cent small mononuclears and 4 per cent large mononuclears. She passed a loose stool at 3:15 p. m. At 8 p. m. the temperature was 101 F. and the pulse rate was 92. She experienced slight nausea two or three times after the administration of the atropine. She tolerated water well. During the evening there was considerable headache, which was relieved by 1 Gm. of acetylsalicylic acid given at 9 p. m. The next morning the patient's condition was normal except for weakness. She passed a loose stool at 10 a. m. The white blood count was 4,500 at 10 a. m., with 85 per cent polymorphonuclears, 12 per cent small mononuclears, and 3 per cent large mononuclears. The temperature was 97.4 F. and the pulse rate was 72 at 8 a. m. Camphorated tincture of opium in a dose of 4 cc. was given at 6:10 p. m. for diarrhea. She passed a stool at 10 p. m. All the symptoms were gone the next morning, and the patient was discharged.

*Enterocolic Type.*—A youth, aged 21, on the morning of April 18, 1932, had a "cold in the head," which was worse the next day but improved on April 20. About 4 a. m. on April 21 he had cramps in the upper part of the abdomen and thought that he would have felt better if he could have belched. At 6 a. m. he passed a soft stool, and at 10 a. m. he passed a loose stool without tenesmus, blood or visible mucus. The stool was darker than normal. During the morning there were malaise and a dull frontal headache. I saw him at 11 a. m. because of severe cramplike pain in the upper part of the abdomen. He looked quite ill. The mucous membrane of the nose was slightly swollen, and there was a mucous discharge. There may have been a slight swelling of lymphoid tissue of the throat. The anterior and right posterior cervical lymph nodes were swollen but were not tender. The sinuses were not tender, but the right maxillary sinus was hazy. The temperature was 98.4 F., and the pulse rate was 88. The systolic and diastolic blood pressures were 92 and 66 respectively when the patient was in a recumbent position (they had been 104 and 72 on Oct. 1, 1931). The white blood count was 11,300. A differential count showed 89 per cent poly-



morphonuclears, 6 per cent small mononuclears, 2 per cent large mononuclears, 2 per cent transitionals and 1 per cent basophils. The oculocardiac reflex showed a slowing of the pulse rate from 88 to 72. The blood pressure when the patient was standing was 101 systolic and 81 diastolic. There was no dizziness. Atropine in a dose of 0.0012 Gm., given at 11:15 a. m., relieved the pain, and the patient left the office at 3 p. m. The next morning he reported that he had passed loose stools twice during the afternoon and evening and again at 7:20 a. m. He experienced slight pain in the upper part of the abdomen after meals. Weakness was the only other symptom. The white blood count was 5,750 at 11:30 a. m. The differential count was unsatisfactory.

*Gastric Type.*—A girl, aged 17, had a dull frontal headache and an aching through the eyes at 4 p. m. on Dec. 12, 1931. She vomited four or five times during the night; there was a dull generalized headache; she felt very dizzy on rising. There was slight abdominal soreness with heaviness after meals. A normal stool was passed on December 13. She was admitted to the hospital at 11 a. m. on December 14, with a temperature of 97 F. and a pulse rate of 80. Sodium nitrite in a dose of 0.12 Gm. produced no change in the dizziness. One cubic centimeter of epinephrine given intramuscularly at 4:30 p. m. improved this symptom. One cubic centimeter of a 3 per cent solution of ephedrine sulphate was given orally. This was followed by some nervousness and palpitation. The patient received 0.06 Gm. of phenobarbital at 9:30 p. m. Tincture of belladonna relieved the epigastric soreness and heaviness which began a half hour after supper. The temperature was 98.6 F. and the pulse rate was 88 at 8 p. m. The patient passed a hard stool that night. The next morning there was burning in the epigastrium after breakfast. On December 16 dizziness was the only symptom; this lasted ten days. There was no fever. The patient was discharged at 10 a. m. on December 17.

*Neurocirculatory Type.*—A girl, aged 19, had a dull frontal headache, shifting pain in the lower part of the abdomen, nausea and slight vertigo on the afternoon of April 22, 1932. After passing a constipated stool she felt better, and the next day her condition was normal. At noon on April 25 the frontal headache returned and was worse than before. There were dizziness and a chilly feeling. There was no stool from April 22 until she was seen on April 25 at 5:30 p. m. The white blood count was 11,650. A differential count showed: polymorphonuclears, 70 per cent; small mononuclears, 21 per cent; large mononuclears, 4 per cent; transitionals, 1 per cent; basophils, 5 per cent. The systolic and diastolic blood pressures were 106 and 74 respectively when the patient was in a recumbent position, and the pulse rate was 80. When the patient was standing the immediate blood pressure was 138 systolic and 92 diastolic and the pulse rate was 76; after one minute the blood pressure was 104 systolic and 82 diastolic. Epinephrine increased the dizziness. Atropine in a dose of 0.0012 Gm. was given at 5:34 p. m. The patient was dizzy most of the evening but slept well. The headache was gone the next morning. Except for a slight weakness she felt well, and was discharged at 9 a. m. The maximum temperature was 98 F.

*Typhlo-Appendical Type.*—A girl, aged 20, felt dizzy, chilly and weak and had aching and sharp pain in the middle part of the abdomen at 9 a. m. on April 26, 1932. There had been a normal stool the night before. She was admitted to the hospital at 7 p. m. with a temperature of 100 F. and a pulse rate of 118. The cervical lymph nodes were unaffected; the sinuses were clear and were not tender. The mucous membrane of the nose was slightly red on the left side. The throat did not relax well. Abdominal examination showed a slight tenderness over the cecum, the terminal part of the ileum, McBurney's point and the transverse,

descending and sigmoid colon. Treatment with heptylresorcinol, a salt water enema and a heat pad was instituted. The temperature was 102 F. at 8 p. m. on April 27 and was within normal range on the morning of April 29. On April 27 examination of the abdomen gave negative findings; the only symptom was slight abdominal soreness on movement. On April 28 the patient felt well in spite of fever; the face was flushed. On April 29 she felt even better; the flush was gone. She was discharged at 6:30 p. m.

*Colic Type.*—A youth, aged 20, had a "stomach ache" while walking up the hill from town at 11:30 p. m. on Feb. 24, 1933. He took sodium bicarbonate and a cathartic during the night because he thought that he might feel better if the bowels would move. He came to the hospital at 7:30 a. m. on February 25. The temperature was 99.4 F., and the pulse rate was 78. A heat pad failed to give relief. At 9 a. m. a hypodermic injection of 0.0012 Gm. of atropine sulphate and 0.06 Gm. of codeine was given. This gave little relief. The severe aching pain

TABLE 2.—*Leukocytosis and Leukopenia in Polytropous Enteronitis*

Leukocytosis		Leukopenia		Leukocytosis Followed by Leukopenia	
White Blood Cells per Cu.Mm.	Time After Onset	White Blood Cells per Cu.Mm.	Time After Onset	White Blood Cells per Cu.Mm.	Time After Onset
13,000	2¾ hrs.	3,200	A few hours?	{11,300	{ 7 hrs.
9,500	11 hrs.	6,600	Same day	{ 5,750	{31 hrs.
11,500	12 hrs.*	3,500	12 hrs.	{13,700	{Same day
8,300	12 hrs.*	5,900	21 hrs.?	{ 5,800	{14 hrs. later
8,500	17½ hrs.	4,600	21 hrs.		
9,300	21 hrs.?	4,100	32 hrs.		
8,650	24 hrs.*	3,900	2 days		
12,150	3 days	6,000	2 days		
8,300	4 days				

\* Approximately.

was well localized just above the umbilicus. There was tenderness over the rectus abdominis muscles, particularly just above the umbilicus. The patient said that the heat seemed to aggravate the distress, so the heat pad was removed. The pain was worse when the patient sat or stood. He slept the latter part of the morning; at noon a hot salt water enema was given. There was some dysuria when the bowels moved after the enema. The patient seemed to be more comfortable in the afternoon and slept for some time. The temperature and pulse rate were 99.8 F. and 88 respectively at 3 p. m.; at 8 p. m. they were 99.8 F. and 68, and at 9 p. m. they were 99 F. and 68. At 1:15 a. m. on February 26 the pain was worse. Another hypodermic injection of atropine and codeine gave some relief. That day the patient was fairly comfortable except for weakness and abdominal soreness on rising. The temperature ranged from 97 F. to 98.6 F., and the pulse rate ranged from 60 to 66. One and three-tenths cubic centimeters of tincture of belladonna was given three times a day before meals. On February 27 the patient was better and was discharged with instructions to continue taking the belladonna until the distress was gone. On March 4 he reported that he had not noticed any definite abdominal soreness for two or three days but that there was still some weakness. He said that he feared a recurrence of the pain and was continuing to take 1.3 cc. of tincture of belladonna before meals.

Cases of obscure dull headache, dizziness and nervousness, malaise, anorexia, vague abdominal distress and obscure gastro-intestinal complaints frequently occurred in close association with epidemics and sporadic cases of typical polytropic enteronitis. Many of them were abortive cases of this disease. They are not described here because they were not typical enough and because their relationship was not sufficiently clear to justify their inclusion in the present report. When obscure complaints of this type present themselves, polytropic enteronitis should be kept in mind in making the differential diagnosis.

#### TREATMENT

In the general treatment prompt, thorough evacuation of the gastro-intestinal tract, with abstinence from food for twenty-four hours is indicated. Drastic cathartics are contraindicated. Magnesium sulphate taken by patients on their own initiative definitely aggravated the intestinal symptoms. Magnesium oxide, magnesia magma, cascara sagrada, sodium phosphate and other mild laxatives are ineffectual in controlling the symptoms. Kaolin and mineral oil emulsions definitely aggravate the intestinal symptoms.

I have found no drug to compare with castor oil. An ounce mixed with an equal quantity of orange juice is stirred together with a level teaspoonful of sodium bicarbonate and is given while effervescing. A cleansing enema consisting of two teaspoonfuls of salt to a quart of tap water at a temperature of from 100 to 108 F. will assist materially. If there is much nausea or vomiting it will be necessary to give from 0.0006 to 0.0012 Gm. (from  $\frac{1}{100}$  to  $\frac{1}{50}$  grain) of atropine hypodermically. The latter dose is usually necessary to produce the desired effect. From fifteen to thirty minutes later the castor oil and enema may be given. Castor oil seems to have little effect on the course of the disease after the first twelve to twenty-four hours.

When the patient begins to eat he should be allowed only a soft bland diet. Acid foods, highly seasoned foods, and foods with a high residue may aggravate the diarrhea or cause its return. McLean<sup>3</sup> advised against the use of milk for children with this condition, but I use it freely for young adults. Water should be given as freely as it is tolerated, but should not be cold. Rest in bed is necessary in the acute phase only, unless other conditions indicate a more prolonged inactivity. I have never known any harm to come from allowing the patient to get up as soon as he felt like it. Complicating subacute appendicitis or the severe colic type of the disease may require that physical activities be restricted for from one to two weeks.

From 4 to 6 capsules (0.15 Gm. each) of heptylresorcinol given with the castor oil, followed by from 2 to 4 capsules taken every four hours

the first day, seems to be of value in helping the castor oil check the symptoms. After twenty-four hours it seems to be ineffectual.

Although sodium ricinoleate is not nearly so effectual as castor oil at the beginning of treatment, from 5.3 to 8 Gm. (from 80 to 120 grains) given daily in divided doses seems to act as a buffer in the intestinal tract against the infection, particularly in the milder cases. I should advise its use if postprandial distress follows the subsidence of the more acute symptoms, with the dose reduced to 0.3 Gm. (5 grains) given four times a day.<sup>37</sup> It seems to lack the laxative effect of castor oil, thus exploding an old theory that the laxative effect of castor oil was due to saponification of its triglyceride of ricinoleic acid.<sup>37</sup> This probably accounts for the fact that sodium ricinoleate cannot replace castor oil in initiating treatment.

For nausea, vomiting and pain from 1.3 to 2 cc. (from 20 to 30 drops) of tincture of belladonna given at once and 1.3 cc. given every four hours perorally is of value. If this is vomited one may resort to atropine given hypodermically. Ethyl aminobenzoate, sodium bicarbonate and peppermint appear ineffectual, although peppermint is sometimes given with belladonna as a flavor and adjuvant because it is claimed to relax gastric peristole. Benzyl benzoate is often disagreeable, although it is flavored with almond oil. This drug and calcium *o*-benzyl-oxybenzoate are often vomited before they have a chance to take effect on the vomiting and distress. Sodium nitrite, given in doses of from 0.06 to 0.18 Gm. (from 1 to 3 grains), may help to control nausea but may increase dizziness. It affects abdominal distress to a lesser extent than the other drugs mentioned or not at all, suggesting that the distress is not due entirely to a spasmodic condition.<sup>38</sup> I used nitroglycerin on only one occasion. Codeine in doses of 0.06 Gm. (1 grain) is a valuable adjuvant to the atropine, particularly if there is pain. A hot water bottle at a temperature of 120 F. or an electric heat pad is useful for the pain but may increase the nausea. In the colic type, rapid relief is obtained with atropine, codeine and heat, followed in from fifteen to thirty minutes by a salt water enema. The patient should be warned that he may be slightly more nauseated for a while after the enema. The administration of mineral oil or its emulsions to patients with constipation is to be discouraged, since they may increase the flatulence and distress.

Although I have given much calcium carbonate, I am not convinced that it has any value in the diarrhea of this condition, but it may be

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37. Sollmann, T.: *A Manual of Pharmacology*, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 210.

38. Beams, A. J.: Nitrites in Spasmodic Conditions of Gastro-Intestinal Tract, *J. A. M. A.* **97**:907 (Sept. 26) 1931.

given in doses of 2 Gm. ( $\frac{1}{2}$  drachm) every four hours. The same is true of bismuth subcarbonate. Bismuth subnitrate seems to excel bismuth subgallate; possibly this is due to the nitrate ion, if Steiglitz<sup>39</sup> is correct in his theory of the fate and action of the drug in the intestine. Bismuth subnitrate is given in doses of from 1 to 2 Gm. (15.4 to 30.8 grains) every two to four hours. I usually give 2 Gm. every two hours until the diarrhea is checked, and then every four hours for a full day. I have never noticed any untoward effects from bismuth in such doses in cases of this type. With this I give camphorated tincture of opium in doses of 4 cc. (1 drachm) not oftener than every four hours. If these drugs are given before the end of the second day the diarrhea seems to be prolonged and the cramps worse.

For dizziness, a snugly applied scultetus abdominal binder or adhesive strapping is most effective. One cubic centimeter (15 drops) of epinephrine hydrochloride given hypodermically usually gives relief. If it does, 0.02 Gm. ( $\frac{3}{8}$  grain) of ephedrine should be given every four hours until 4 p. m. If it is given after that time, it may cause sleeplessness in some patients. For nervousness and restlessness, which are common in the neurocirculatory type of the disorder, I have found phenobarbital useful in doses of from 0.015 to 0.03 Gm. (from  $\frac{1}{4}$  to  $\frac{1}{2}$  grain) given four times daily, and for insomnia a single dose of from 0.06 to 0.18 Gm. (from 1 to 3 grains) given just before bed time is effective.

Acetylsalicylic acid in doses of from 0.3 to 1 Gm. (from 5 to 15 grains) is the most useful remedy for headache. Although I have used the ice-cap, I doubt the advisability of its use, particularly if there are respiratory symptoms. The nose and throat should be treated as indicated in patients with respiratory symptoms.

#### MORBIDITY

That this disease is becoming a public health problem of first magnitude is indicated by the widespread reports coming to me through the United States Public Health Service and other sources. The importance of the disease has become rapidly apparent in summer camps and national parks and in institutions such as colleges. Even in these groups the magnitude of the problem is not always appreciated. In spite of the easy access of patients to my service at all times, surveys indicate that I probably saw only about one fifth of the cases which occurred during the local epidemics and that at least from one third to one half or more of the student body is affected annually. In the general population the significance of the disorder is rapidly lost on account

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39. Steiglitz, E. J.: Bismuth Subnitrate in Treatment of Arterial Hypertension, *J. A. M. A.* **95**:842 (Sept. 20) 1930.

of the few persons who seek medical advice because of it. How often have I heard: "It's just something I ate" or "It's only indigestion." This attitude has doubtless been a factor in increasing the mortality from appendicitis.<sup>40</sup> So long as there exists so generally a condition which never seems to kill, in spite of the acuteness of the symptoms, is it not natural that a careless attitude should be engendered? Efforts to educate the public must be redoubled. Physicians must attempt to make a rapid and accurate diagnosis of Spencer's disease in order to prevent unnecessary surgical measures and must try to discover some method of effectively controlling the morbidity.

#### SUMMARY

There apparently exists quite generally a clinical entity which has erroneously been called gastro-intestinal influenza, food poisoning, ptomaine poisoning, biliousness, acute autointoxication, dietary indiscretion and the like. Considerable information concerning the etiology, epidemiology, pathogenesis, symptomatology and differential diagnosis of this condition has been gathered from observations on more than a thousand cases seen within the past seven and a half years. A distinctive name is now proposed. The present report is based on a study of about 750 college students who had from one to six or more attacks between September, 1927, and June, 1932. Much more work is needed to settle some points, particularly those concerning the etiologic agent and the pathologic condition which it produces.

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40. Bower, J. O.: Mortality of Acute Appendicitis, *J. A. M. A.* **99**:1765 (Nov. 19) 1932. Lowe, H. A.: Causes of High Mortality in Appendicitis, *J. Missouri M. A.* **28**:525, 1931.

# UNCOMPLICATED SYPHILITIC AORTITIS

## DIAGNOSIS, PROGNOSIS AND TREATMENT

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The questions of diagnosis and of prognosis of untreated syphilitic aortitis with aneurysm or aortic regurgitation require no elaboration. Two reports from this clinic<sup>1</sup> have shown that by appropriate treatment of these conditions, it is possible materially to prolong life and to alleviate symptoms in a considerable proportion of cases. In these reports and elsewhere, the *a priori* opinion has been offered that the results of treatment should be even more satisfactory if treatment could be administered while the aortitis was still uncomplicated by valvular incompetency or aneurysmal sacculation. A demonstration of this fact, if true, depends, however, on the accuracy of diagnosis of uncomplicated aortitis.

Although it has been generally agreed that this diagnosis could be made occasionally in a patient with fully developed symptoms and signs, and although some clinicians, as for example Albutt,<sup>2</sup> have insisted that it might be made with far greater frequency than is customary, there is still a prevalent impression that in the absence of aneurysmal dilatation or aortic insufficiency, syphilitic aortitis cannot be recognized with accuracy during life. The skepticism is of course due to the

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From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital.

Read before the Association of American Physicians, Washington, D. C., May 9, 1933.

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1. Moore, J. E., and Danglede, J. H.: The Treatment of Cardiovascular Syphilis: A Study of the Duration of Life in 141 Treated and Untreated Patients with Aortic Regurgitation and Aneurysm, *Am. Heart J.* **6**:148, 1930. Moore, J. E.; Danglede, J. H., and Reisinger, J. C.: Treatment of Cardiovascular Syphilis: Results Obtained in Fifty-Three Patients with Aortic Aneurysm and in One Hundred and Twelve with Aortic Regurgitation, *Arch. Int. Med.* **49**:879 (June) 1932.

2. Allbutt, T. C.: Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, 1915.

similarity of symptoms and physical signs resulting from syphilitic aortitis, aortic atherosclerosis and essential hypertension.

In an earlier communication,<sup>3</sup> one of us (J. E. M.), with Danglade and Reisinger, discussed the diagnosis of uncomplicated syphilitic aortitis on the basis of a study of the correlation of clinical and pathologic findings in 105 patients in whom the existence of this lesion had been recognized during life in only a few, but proved at post-mortem examination in all. Seven diagnostic criteria were listed: (1) teloradiographic and fluoroscopic evidence of aortic dilatation; (2) increased retromanubrial dulness; (3) a history of circulatory embarrassment; (4) a tympanitic bell-like, tambour accentuation of the aortic second sound; (5) progressive cardiac failure; (6) substernal pain, and (7) paroxysmal dyspnea. The belief was expressed that in a patient with a recognized late stage of syphilis (whether or not the Wassermann reaction of the blood is positive) without disease of the mitral valve, the presence of any three of these criteria is strong evidence in support of a definite diagnosis of uncomplicated syphilitic aortitis, while the presence of any two of them renders the diagnosis probable.

We realized that in order to validate this position it would be necessary to follow a series of patients in whom this diagnosis had been made during life, in order to determine to what extent the more definite lesions of aneurysm or aortic regurgitation developed, the cause of death, and the effect, if any, of treatment on the course of the disease. The subject matter of the present communication is a consideration of these points.

#### OBSERVATIONS

*The Material of the Study.*—We report on the status of 115 patients with a late stage of syphilis in whom the clinical diagnosis of syphilitic aortitis was made. Each of these patients was examined by several observers, and the majority by one of us. We limit ourselves to a discussion of three main points: (1) the extent to which the ultimate outcome justified the original diagnosis; (2) the extent to which the outcome was influenced by treatment, and (3) the influence of associated hypertension on the outcome. Because of lack of space we omit a consideration of the evidence on which the diagnosis of uncomplicated syphilitic aortitis was based in these 115 patients. This will appear in a later communication. At present it must suffice to say that all of them were definitely syphilitic, that none had disease of the mitral valve, and that all had at least two, and most of them more, of the seven diagnostic criteria listed.

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3. Moore, J. E.; Danglade, J. H., and Reisinger, J. C.: Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm: Comparison of Clinical and Necropsy Observations in One Hundred and Five Patients, *Arch. Int. Med.* **49**:753 (May) 1932.



*Validity of the Diagnosis of Uncomplicated Aortitis as Determined by the Subsequent Course.*—We have made every effort to follow these patients with frequently repeated physical and roentgen examinations. Those who regularly attended the clinic have been reexamined at periodic intervals; others have been persuaded by the efforts of social service to return for study. Deaths have been verified by examination of the records of our own and of several other of the large hospitals in Baltimore and of the death certificates issued by the City Health Department. The success of this type of follow-up is apparent from the fact that of the 86 living patients, none has been under observation for less than two years, and the average period of observation exceeds eight years.

If in a patient with a diagnosis of uncomplicated aortitis—the existence of saccular aneurysm or aortic regurgitation having been

TABLE 1.—*Outcome in 115 Patients with Uncomplicated Syphilitic Aortitis (Without Reference to Treatment)*

Total Number Cases	Living			Dead			
	Symptom-Free; No Progress in Physical or Roentgen-Ray Signs	Showing Progress in Symptoms or Signs	Showing Development of Aortic Regurgitation or Aneurysm	Of Aneurysm or Aortic Regurgitation	Of Other Forms of Cardiovascular Syphilis (Proved)	Probably of Cardiovascular Syphilis	Of Other Known or Unknown Causes
115	41	35*	10†	7	2	6	14‡

\* Of these patients, 7 are wholly or partly incapacitated by progressive cardiac failure.

† In 2 instances the clinical diagnosis is questionable.

‡ In 3 patients aortic regurgitation developed before death.

excluded by all available means—one of these two conditions subsequently develops, it may be assumed that the original diagnosis of aortitis was correct, whether or not the lesion is verified at section. If aneurysm or aortic insufficiency does not develop, the only absolute proof of the correctness of the original diagnosis is the evidence of necropsy. Strong presumptive proof, however, is offered if the symptoms and physical signs originally present increase in severity and extent, and particularly if congestive heart failure for which there is no other obvious explanation develops.

During the period of this study, the outcome in our 115 patients, leaving out of consideration for the moment the amount of treatment administered, is as shown in table 1. In 22 of the total number, or 19.1 per cent, indubitable evidence of cardiovascular syphilis developed, testifying to the correctness of the original diagnosis. In these, saccular aneurysm developed in 8 (2 now living, 6 dead) and aortic insufficiency in 12 (8 still living, and 4 dead); 2 others, who died of congestive heart failure, were found at necropsy to have syphilitic aortitis complicated by myocarditis.

Presumptive evidence of the validity of the original diagnosis is furnished by 41 additional patients, or 35.6 per cent. Of these, 6 died elsewhere than under our observation of some form of disease of the heart variously diagnosed by the attending physician, within an average interval of thirty months after the diagnosis of aortitis had been made, i. e., within so short a time that, considering the demonstrated absence of any form of heart disease other than cardiovascular syphilis at the time of the original examination, death may be presumed to have occurred from that cause. Thirty-five are still living in whom symptoms, or more commonly physical or roentgen ray signs, originally present have grown more marked, and of these, 7 are wholly or partly incapacitated by progressive cardiac failure.<sup>4</sup>

Thus, the original diagnosis seems thoroughly justified by virtue of the fact that, disregarding the amount of treatment given, there has been definite or presumptive evidence of progression of the lesion in 54.7 per cent of the 115 patients studied. This portion of the study is confirmatory of our already expressed conclusion, based on a correlation of necropsy and clinical findings,<sup>3</sup> that the diagnosis of syphilitic aortitis can be accurately made in a considerable proportion of cases, even in the absence of aortic regurgitation or aneurysm.

*Results of Treatment in Uncomplicated Syphilitic Aortitis.*—In table 2 appear the results of treatment of patients with uncomplicated aortitis, subdivided into two groups on the basis of the amount of treatment given. The outcome is expressed in the simplest possible terms to show the mortality rate (including deaths from all causes) and the number of patients in each group in whom incontrovertible clinical evidence of cardiovascular syphilis had developed in the form of aortic regurgitation or saccular aneurysm, or who had certainly or probably died of cardiovascular syphilis. The data indicate that untreated or inadequately treated syphilitic aortitis offers a grave prognosis. It also appears that aneurysm or aortic regurgitation (especially the latter) may develop in spite of adequate treatment (8 of 47 patients in the best treated group). This is not surprising. Indeed, in some instances it is probable that the development of aortic regurgitation is actually hastened by treatment. The valve leaflets may already be involved by the inflammatory process, but not yet be so distorted as to produce incompetency, before treatment is begun. With the healing effect of treatment, inflammation is replaced by scar tissue, and distortion and subsequent valvular incompetency appear earlier than would

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4. The fact that cerebral hemorrhage was the cause of death in 4 of the 14 patients recorded as dying of some other cause than cardiovascular syphilis exemplifies the frequent association of syphilitic aortitis with a more generalized syphilitic vascular involvement.

otherwise have been the case. This is not, however, necessarily disastrous. As Stokes<sup>5</sup> has aptly put it, a progressive disability is exchanged for a static one.

The average duration of life dating from the time of the diagnosis of aortitis, in the living well treated patients of this series, exceeds eight years, as compared with the average of somewhat over five years for a similarly treated group of patients with aneurysm or aortic regurgitation. Many more of the patients with uncomplicated aortitis are free from symptoms and able to work than are those in the earlier group. It seems certain from our data that the treatment of uncomplicated syphilitic aortitis relieves symptoms, maintains physical efficiency, prevents the appearance of graver forms of cardiovascular syphilis and prolongs life in a considerable proportion of cases. By

TABLE 2.—*Relationship of Antisyphilitic Treatment to the Outcome of Uncomplicated Syphilitic Aortitis*

Treatment	Total No. of Patients	Deaths, All Causes		Incidence of Graver Forms of Cardiovascular Syphilis (Aneu- rysm, Aortic Insufficiency or Death from Congestive Heart Failure), Certain or Probable	
		Patients	Per Cent	Patients	Per Cent
Fewer than 12 injections of an arsphenamine product with heavy metal preparation in interim .....	45	19	42.2	14	31.1
More than 12 injections of an arsphenamine product with heavy metal preparation in interim .....	70	10	14.2	14	20.0

comparison with the results of treatment in patients who have already developed aneurysm or aortic regurgitation, the results in uncomplicated aortitis are vastly better.

*Influence of Essential Hypertension Complicating Syphilitic Aortitis on the Outcome.*—On the basis of numerous studies, it is clear that hypertension is not caused by syphilitic aortitis, and that the association of the two conditions is relatively infrequent. As a matter of fact, essential hypertension occurs in patients with aortitis with about the same frequency as in nonsyphilitic patients in groups of analogous age. We discussed elsewhere<sup>3</sup> the diagnostic difficulties which arise when the two conditions are associated, and concluded that in spite of their coexistence the diagnosis of syphilitic aortitis may often be made with accuracy. This statement receives confirmation from the present study, which also provides another fact of importance, i. e., that the prognosis in syphilitic aortitis is much worse when hypertension from any cause

5. Stokes, J. H.: *Modern Clinical Syphilology*, Philadelphia, W. B. Saunders Company, 1926.

is a complicating feature. These data appear in table 3. Of the total 115 patients with uncomplicated aortitis, 31 had hypertension (systolic pressure, 150 or over), 74 did not, and regarding 10, information is lacking. In the group with hypertension, aneurysm or aortic regurgitation subsequently developed in 10 (32 per cent). In those without hypertension, this occurred in 9 (12 per cent). The mortality rate and the incidence of the graver forms of cardiovascular syphilis are approximately twice as great in patients with, as in patients without, a complicating hypertension.

TABLE 3.—*Influence of Hypertension on the Outcome of Uncomplicated Syphilitic Aortitis*

	Total Number of Cases	Mortality, per Cent	Percentage of Incidence of Cardiovascular Syphilis (Aneurysm, Aortic Regurgi- tation or Death from Congestive Heart Failure), Certain or Probable
Patients with hypertension.....	31	32.2	35.4
Patients without hypertension.....	74	19.0	17.5
Patients with no data as to hypertension.	10	50.0	40.0

#### SUMMARY AND CONCLUSIONS

1. By uncomplicated syphilitic aortitis is understood a diffuse supralvalvular involvement of the aortic wall, with or without diffuse dilatation, but without valvular incompetency or saccular aneurysm.

2. Seven criteria for the clinical diagnosis of this condition are listed.

3. The accuracy of clinical diagnosis has been tested by the prolonged study of 115 patients in whom this diagnosis had been made during life.

4. In 19.1 per cent of this group of patients, indubitable graver forms of cardiovascular syphilis subsequently developed, and in an additional 35.6 per cent, presumptive evidence of the correctness of the original diagnosis was furnished by the subsequent course.

5. The clinical diagnosis of uncomplicated syphilitic aortitis can be accurately made in a considerable proportion of patients with late syphilis.

6. A consideration of the results of treatment indicates that symptoms may be relieved, physical efficiency maintained, the appearance of the graver forms of cardiovascular syphilis prevented, and life prolonged in a considerable proportion of patients with uncomplicated aortitis, and that these results are better than those obtainable after the development of aortic regurgitation or aneurysm.

7. Hypertension complicating syphilitic aortitis doubles the mortality rate and the incidence of development of the graver forms of cardiovascular syphilis.

# Correspondence

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## MODIFIED DEXTROSE TOLERANCE TEST

*To the Editor:*—In the July, 1933, issue of the ARCHIVES, page 147, appeared an article by Dr. H. T. Ricketts, "An Appraisal of the Modified Dextrose Tolerance Test," which contains a number of misleading statements on which I should like to comment.

1. In an article, entitled, "Modification of the Dextrose Tolerance Test as an Index of Metabolic Activity of the Liver," by Lewis Gunther, John B. Lagen, William J. Kerr and me (ARCH. INT. MED. **46**:482 [Sept.] 1930), we claim that a modification of the dextrose tolerance test produces lower blood sugar values in patients with hepatic disease than in normal persons; this is substantiated by the figures of Dr. Ricketts. His graphic chart shows that, with two exceptions, the lowest blood sugar value in the curves of patients with hepatic damage is lower than the lowest figures in the normal and "doubtful" groups. The first exception (11) is in a case of carcinoma of the pancreas with obstructive jaundice, and we think that it is an advantage of the test that jaundice without intrinsic injury to the liver gives negative results. The other exception (14a) is a second test in a patient who recovered and whose galactose tolerance and excretion of bromsulphalein had returned to normal.

2. Our dividing line between normal and abnormal cases "in the vicinity" of 70 mg. per hundred cubic centimeters with the Folin and Wu method was selected empirically from a study of sixty-four cases on the basis of clinical findings and the rose bengal dye excretion test. If Folin's new method of blood sugar determination is used, the dividing zone must again be established empirically, and not by simple subtraction of 20 mg., because this method excludes noncarbohydrate-reducing substances of the blood. Quantitatively, by far the most important of these substances is glutathione, which has been shown to increase in the blood of normal persons following injections of insulin (Cahane, M.: *Comp. rend. Soc. de biol.* **110**:644, 1932) and to be diminished in the blood of patients with many hepatic diseases, such as jaundice and cirrhosis (Binet, L., and Arnaudet, A.: *Comp. rend. Soc. de biol.* **110**:24, 1932; Villaret, M.; Justin-Besançon, L.; Even, R., and Drilhon, M.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:775, 1932; Varela, B.; Munilla, A., and Duomarco, J.: *Comp. rend. Soc. de biol.* **111**:533, 1932). Consequently, the results of the modified dextrose tolerance test may be rendered more decisive by using a method of blood sugar determination, such as the Folin and Wu method, which includes in its readings variations of glutathione, because, as indicated by the cited references, such variations in many hepatic diseases enhance the changes in blood sugar during the test. From Dr. Rickett's cases an empirical dividing line for the new Folin method suggests itself at about 30 mg.

At present, a survey of recent cases in which tests of the hepatic function were performed is being made at the University of California Hospital. This survey, so far, reveals agreement of the modified dextrose tolerance test with the clinical picture and with the rose bengal test in twenty-six of thirty patients with and without hepatic disease. In the remaining four cases, the clinical picture is in accord with the modified dextrose tolerance test in two instances and with the dye excretion test in two cases. We consider this as further evidence that 70 mg. is an approximately correct dividing zone if the Folin and Wu method is used. We pay little attention in the interpretation of the test to insulin reactions, because we

have seen the blood sugar of patients with an habitually low blood sugar level reach levels sometimes under 30 mg. without reactions, while the reverse is true for patients with an habitually high blood sugar level.

3. A just criticism of the test from Dr. Ricketts' blood sugar curves might be that the "spread" between normal and pathologic cases is not great enough; on the one hand, the five patients with the lowest blood sugar in the normal and "doubtful" groups (cases 2, 3, 5, 7 and 9) have conditions such as cardiospasm, chronic vomiting or pyloric stenosis, leading to disturbances of nutrition and low hepatic glycogen, which reduces the ability of the liver to release dextrose in case of impending hypoglycemia, and, on the other hand, in his pathologic cases the patients had only mild hepatic insufficiency, since all but one (case 14) were found to have normal results with a dye excretion test, which is accepted as a valuable diagnostic aid by most medical writers.

4. From a comparison of the bromsulphalein test with the modified dextrose tolerance test in Dr. Ricketts' small number of cases, it is apparent that the latter gave more accurate indications of hepatic damage. At the same time, it is significant that the lowest blood sugar level (11 mg.) was obtained and the test had to be interrupted owing to a marked insulin reaction in the only patient who had an abnormal retention of the dye. Later, when the excretion of bromsulphalein became normal, the lowest blood sugar level following the modified dextrose tolerance test also increased to the level obtained by Dr. Ricketts in his normal cases, and at this time there was no necessity of interrupting the test. This indicates a good agreement between the two tests.

5. In discussing the theoretical aspects of the modified dextrose tolerance test, Dr. Ricketts mentions that the blood sugar curve following the administration of 100 Gm. of dextrose may end in hypoglycemia in normal persons and that therefore the giving of 50 Gm. of this sugar with 20 units of insulin is even more likely to produce hypoglycemia. The reason for hypoglycemia in the first case is that 100 Gm. of dextrose is a heavy strain on the sugar-assimilating organs which are stimulated to utilize increased amounts of dextrose from the blood. When the 100 Gm. given is used up, overfunctioning of these organs still goes on, so that temporary hypoglycemia results. On the contrary, 50 Gm. of sugar covered by 20 units of insulin represents a comparatively light load which causes a much lesser stimulation of the sugar-assimilating organs.

We realize that opinions as to the clinical usefulness of our test may differ, especially since it is based on carbohydrate metabolism in which several extra-hepatic factors play an important part, but we cannot pass in silence a denial of the fundamental facts involved. This is especially so since our clinical work was substantiated by Morawitz and Mancke (*Klin. Wchnschr.* **11**:623, 1932), who also performed the test on fifteen normal persons, and by Milbradt (*Arch. f. Dermat. u. Syph.* **164**:399, 1931), who, among a hundred cases, tested ten patients without hepatic disease. In addition, our clinical findings were duplicated in animals with experimental injury to the liver (*ARCH. INT. MED.* **50**:58 [July]; 257 [Aug.] 1932).

T. L. ALTHAUSEN, M.D., San Francisco.

*To the Editor:*—My contention (*ARCH. INT. MED.* **52**:147 [July] 1933) that the modified dextrose tolerance test is not a satisfactory measure of the metabolic function of the liver was based on results obtained by performing this test on ten patients who were considered to have normal livers and on four patients with frank hepatic disease. In nine of the ten normal patients, definite chemical and clinical hypoglycemia developed—the response said by Dr. Althausen to be characteristic of disease of the liver. Three of four of the patients with hepatic disease also

exhibited a terminal drop in blood sugar which was somewhat, but not markedly, lower than in most of the normal cases. There was, therefore, no essential difference between the behavior of the normal and the abnormal groups.

The important criticisms of this work which are raised in Dr. Althausen's present communication revolve about two questions: 1. Were the patients normal? 2. What constitutes hypoglycemia?

1. The "normal" group consisted of patients on the gastro-intestinal service of the Billings Hospital who were being treated for conditions in no recognized way related to the liver and who gave no evidence of hepatic disease. Dr. Althausen's assumption that these patients must have had a low hepatic glycogen simply on the basis of their diagnoses is unwarranted. In accordance with the technic which he originally proposed, all patients in this group had been consuming for several days before the test an adequate diet, which contained from 250 to 300 Gm. of carbohydrate. The group as a whole averaged only 7.6 per cent underweight as computed from the tables of Davenport (*Body Build and Its Inheritance*, Washington, D. C., Carnegie Institution, 1923, publ. no. 329). This can scarcely be called a pathologic deviation. The patient in case 5 (one of nervous vomiting), whose blood sugar dropped to 25 mg. per hundred cubic centimeters, was slightly above normal weight as given by these tables. In none of these patients had there been any acute loss of weight.

It might be added here that so far as the degree of hepatic insufficiency in the pathologic cases is concerned, all of the patients, regardless of the dye excretion test, had suffered damage to the liver sufficient to produce jaundice, which in only one case was due to obstruction.

2. In the original paper by Dr. Althausen and his associates the proposition was made that "terminal hypoglycemia under the conditions of the test meant injury of the liver." Using the Folin and Wu method of analysis, they placed the dividing line between normal and hypoglycemic values at 70 mg. of sugar per hundred cubic centimeters of blood. The new Folin method which I used gives values about 20 mg. lower, so that the dividing line was placed at 50 mg. per hundred cubic centimeters of blood. Dr. Althausen now proposes to apply in my cases a critical level, as determined by the Folin method, of 30 mg. per hundred cubic centimeters of blood. He would thus seem to imply either that the blood sugar must drop to 30 mg. before hypoglycemia may be considered to exist, or that he has abandoned the hypoglycemic concept in this connection altogether. That any normal person in whom a blood sugar of from 30 to 50 mg. develops (Folin method) is in a state of hypoglycemia would seem obvious. If, on the other hand, Dr. Althausen and his colleagues have decided not to use the term "hypoglycemia" in referring to responses of patients with hepatic disease, a statement from them to that effect would be in order.

If the modified dextrose tolerance test depends for its interpretation on estimation of the amount of sugar in the blood, it is difficult to see how Dr. Althausen can justifiably take exception to the use of an analytic method which determines the true blood sugar more accurately than does his own.

With regard to glutathione, investigation of the reference cited by Dr. Althausen to the effect that the amount of this substance in the blood of normal patients is increased by the injection of insulin, yields the following information: Cahane gave 20 units of insulin to two healthy human subjects and followed the blood sugar and total sulphur content of the blood for two hours after injection (no figures are given for the proportion of the total blood sulphur which glutathione constitutes). The blood sugar dropped as anticipated, but the total sulphur increased in one patient by only 2 mg. per hundred cubic centimeters of blood, and in the

other by 1.6 mg. The remainder of Cahane's work was done on two normal dogs, into each of which he injected from 2.5 to 4 units of insulin per kilogram of body weight—a decidedly large dose—and obtained increases of 0.6 mg. and 2.2 mg. of sulphur per hundred cubic centimeters of blood, respectively. Such results are entirely within the limits of error of the method and have no significance in the present connection. Even taking them at their face value, it is impossible to imagine that differences of from 0.6 to 2.2 mg. of glutathione following the injection of insulin could have any material influence on the very much higher figures in which even hypoglycemic blood sugar values are expressed.

While a disregard of insulin reactions in interpreting tests performed on patients with abnormal blood sugars during fasting is understandable, the presence of normal levels during fasting in my patients establishes the significance of their hypoglycemic symptoms, especially since all reactions were accompanied by blood sugars which were undeniably below normal.

The matter of stimulation of the sugar-assimilating organs by dextrose feeding is one largely of speculation. There is, however, direct evidence that a dose of dextrose of even 50 Gm. given by mouth may produce hypoglycemia. Gibson and Larimer (*J. A. M. A.* **82**:468 [Feb. 9] 1924) gave this amount to a patient with renal glycosuria who had a blood sugar during fasting of 58 mg. Three hours later the patient had mild symptoms, and the blood sugar was found to be 40 mg. Moreover, Stenström (*Deutsches Arch. f. klin. Med.* **157**:216, 1927) "in four patients with blood sugars during fasting between 76 and 95 mg. (noted) hypoglycemia about two hours after they had taken 1 Gm. of dextrose per kilogram of body weight, with readings between 46 and 53 mg." If, then, the administration of as little as 50 Gm. of dextrose alone may be followed by hypoglycemia in normal persons, one might expect that the addition of 1,500 cc. of water and 20 units of insulin would accentuate this tendency. Results in my normal cases substantiate this expectation. In answer to Dr. Althausen, therefore, it might be said either that this dosage of dextrose produces a greater pancreatic stimulation than he assumes, or that possibly the insulin is inadequately covered by the sugar given.

With respect to the confirmation of Dr. Althausen's work by other investigators, Morawitz (in whose clinic Dr. Althausen did some of his work) and Mancke give only the average curve for their normals. Their results would be more convincing had they given figures for the individual cases, for a functional test is useful only to the extent that all normal persons can be shown always to respond to it in the same way. Morawitz and Mancke, moreover, accept as a normal reaction a maximum difference of 20 mg. between the blood sugar level during fasting and the lowest blood sugar level. All but three of my normal patients showed differences considerably greater than this. Milbradt, like the authors just mentioned, merely makes a statement about the average of his ten normal patients.

The data obtained by Dr. Althausen on laboratory animals are inconclusive. Reference is made to the article, entitled, "Influence on Carbohydrate Metabolism of Experimentally Produced Hepatic Changes: III. Chloroform Poisoning" (*ARCH. INT. MED.* **50**:257 [Aug.] 1932), in which are given the results of the administration of the modified dextrose tolerance test to rabbits. This test was performed on nine normal rabbits before they were poisoned. Of this number, four (rabbits 804, 824, 832 and 835) responded by a drop in blood sugar of 86, 47, 68 and 50 mg., respectively, from the initial level at the end of three hours. Incidentally, these drops in some cases were greater than those obtained after poisoning, although the initial blood sugar levels were lower in the latter instance. I cannot discover that Dr. Althausen has set up a dividing line between "normal" and "abnormal" responses for rabbits, but such results in normal animals are entirely consistent with mine in normal human beings.



In conclusion, it is evident from both Dr. Althausen's work and my own that the modified dextrose tolerance test usually produces hypoglycemia in hepatic damage. The difficulty is, however, that, in my own hands at least, it also produces hypoglycemia in patients who have normal livers, a fact which has recently received confirmation by Migneco (*Policlinico* **101**:248 [July 15] 1933), who also concluded that the test was not satisfactory. A comparison of the statements made in Dr. Althausen's original article (*ARCH. INT. MED.* **46**:482 [Sept.] 1930) with those contained in his present communication reveals that in the former he refers to "hypoglycemia" as the criterion of hepatic damage, whereas in the latter he merely states that the modified dextrose tolerance test "produces lower blood sugar values in patients with hepatic disease than in normal persons." If the last statement quoted is to be taken at its face value, with no further implications, it represents, granting further substantiation, an interesting contribution to the already existing knowledge of disturbed carbohydrate metabolism in hepatic disorders. If, however, the modified dextrose tolerance test is to be set up as a clinical procedure, with hypoglycemia "under the conditions of the test" as the *sine qua non* for hepatic damage, its usefulness is apt to be largely vitiated by the marked tendency of normal persons to respond by blood sugar levels which are definitely hypoglycemic.

HENRY T. RICKETTS, M.D., Chicago.

*To the Editor:*—After reading Dr. Ricketts' reply to my first letter, I am constrained to make the following further comments:

1. Cahane's work, far from being "within the limits of error," is a confirmation of the work of Zunz (*Compt. rend. Soc. de biol.* **108**:223, 1931).

The rise in glutathione after the injection of insulin in Cahane's work is *not* from 0.6 to 2.2 mg., as stated at the end of the paragraph by Dr. Ricketts, but over ten times that amount (the sulphur coefficient of glutathione is 10.5). In the two human cases this difference amounts to 16 and 22 mg. and is of considerable importance.

2. As to the production of hypoglycemia in *normal* persons with 50 Gm. of dextrose: In the case of Gibson and Lorimer, Dr. Ricketts omitted the important fact that this patient had spontaneous attacks of hyperglycemia with subjective symptoms. Furthermore, this patient had marked renal glycosuria with a blood sugar during fasting of 58 mg. We reported a similar case and pointed this condition out as a source of error in the modified dextrose tolerance test (*Arch. f. klin. Med.* **170**:294, 1931).

Stenström's work was *not* done on normal persons as stated by Dr. Ricketts, but on persons with pluriglandular disturbances (thyroid, ovaries and suprarenals). Two other patients in the same series of six cases had spontaneous attacks of hypoglycemia, in one case with coma for over twenty-four hours. In addition, one of the four cited patients again had renal glycosuria.

3. How convincing the results of Morawitz and Mancke are can be judged from their curves (chart).

Milbradt does *not* "merely make a statement about the average of his normal patients" but specifies that *all* of his ten normal patients had a negative reaction to the test. Since Dr. Ricketts gives no credence to the statements of these investigators, we fail to see how their individual data would be more reliable.

4. It is common knowledge that the sugar metabolism of rabbits is less stable than that of man, and we are content to let our data on laboratory animals speak for themselves. We also wish to point out that Dr. Ricketts arbitrarily selected for criticism one acute experiment with chloroform, omitting to mention two experi-

ments with phosphorus. Of the three experiments, the one with chronic phosphorus poisoning is the most significant one in regard to clinical application.

5. I am unable to discuss the results of Migneco since I cannot find his article under the given reference.

T. L. ALTHAUSEN, M.D., San Francisco.

*To the Editor:*—1. The test proposed by Dr. Althausen is a test of dextrose tolerance. The method of blood sugar analysis which I used determines dextrose, and largely eliminates other reducing substances which might obscure the true picture of dextrose metabolism. The subject of glutathione, therefore, is irrelevant to this discussion, and it already has received more attention than it deserves. It is necessary, however, to reply to Dr. Althausen's last statements in this connection.

(a) All workers in this field are by no means agreed as to whether insulin produces augmentation of the sulphhydryl bodies in the blood. Zunz remarks that Tateishi (*Kyoto-Ikedaigaku-Zasshi* 5:51, 1931) demonstrated sometimes a decrease of glutathione in healthy human subjects after injection of insulin, and both Cahane and Zunz refer to the work of Blanchetière, Binet and Mélon (*J. de physiol. et de path. gén.* 27:1 and 19, 1929), who are said to have observed no influence of insulin on the concentration of glutathione and thionine in the blood. Other investigators did not confirm these results.

(b) My figures taken from Cahane's results, showing an increase of only 0.6 to 2.2 mg. of total sulphur per hundred cubic centimeters of blood after injection of insulin, are correct as given. In the two human cases the increase was 1.6 and 2.2 mg., respectively. Dr. Althausen, in stating that the increase in glutathione was over ten times these figures (because its sulphur coefficient is 10.5), apparently makes the mistake of assuming that all of the blood sulphur is glutathione sulphur, which obviously it is not. Cahane indeed did not determine glutathione as such, and therefore offers no evidence that its level was changed at all.

(c) Cahane stated that the total blood sulphur reaches its height in from one-half to one and a half hours after the administration of insulin and returns to normal at the end of two hours. Thus, at the crucial point in the modified dextrose tolerance test, when hypoglycemia is most marked (at the second to third hour period), the rise in total sulphur produced by insulin has, according to this author, disappeared.

(d) Zunz, who did determine glutathione, and whose results Cahane is alleged to have confirmed, found in dogs a considerable variation in the time of appearance of the glutathione peak and in the time of its return to normal after the administration of insulin. He does not mention the occurrence of a peak at two or three hours. This author stated: "In general, insulin tends indeed to augment the reduced glutathione content of arterial blood, but this increase represents ordinarily only 2 to 7 mg., and only exceptionally reaches 10 to 12 mg., per hundred cubic centimeters of blood" (previous citation, p. 224).

(e) When one considers the facts that insulin produces only such questionable or slight rises in glutathione as previously brought out, that this substance in the concentration in which it exists in normal blood has only about 25 per cent of the reducing power of dextrose as determined by the Folin method\* and that increased amounts of it at a time from two to three hours after the injection of insulin are either minimal or entirely absent, Dr. Althausen's attempt to explain my results on the basis that glutathione is eliminated by the analytic method which I used becomes fruitless.

2. Although the possibility exists that the mild subjective symptoms which the patient of Gibson and Larimer experienced at home were due to hypoglycemia, this was never proved by blood sugar determinations made at such times.

Dr. Althausen has given a grossly inaccurate idea of Stenström's work. The diagnoses in three of the four cases cited were as follows:

Case 1: "Neurasthenia and edema fugans."

Case 2: "Neurasthenia and transitory glycosuria."

(Glycosuria, said to have been found one week previously, was absent in both control determinations. Blood sugar readings for five consecutive half hour intervals during the test were 95 [fasting], 175, 156, 111, 55 and 46, with an excretion of only 0.95 Gm. of sugar in the urine. A diagnosis of renal glycosuria from such findings cannot be established.)

Case 3: "Neurasthenia."

Nowhere does Stenström give the slightest evidence that any of these patients had pluriglandular disturbances.

Case 4 was that of a young woman in whom hypoglycemia developed after the ingestion of 47 Gm. of dextrose. She gave a history of amenorrhea of seven months' duration and was found to have a low blood pressure, a palpable thyroid and a basal metabolic rate of —9 per cent. Stenström, instead of implying that a pluriglandular syndrome was present in this patient, conservatively stated: "Aside from the cessation of the menses, the symptoms of an endocrine disturbance are extremely slight, but the possibility of a pluriglandular disturbance, even in a very mild form, can be excluded" (*Deutsches Arch. f. klin. Med.* **157**: 223, 1927). The two patients with spontaneous hypoglycemia referred to by Dr. Althausen were not subjected to the dextrose tolerance test and have no place in this discussion.

3. The curves of averages given by the German investigators do not prove that each of their normal patients responded to the test by maintaining the blood sugar at nonhypoglycemic levels. The just and time-honored right to demand protocols in scientific investigation has not yet been abrogated.

4. Regarding Dr. Althausen's animal experiments, the marked drop in blood sugar produced by the modified dextrose tolerance test in four of nine rabbits which were used as *normal controls* clearly has nothing to do with the kind of poison which was given later. Moreover, protocols of experiments on normal rabbits published in another article (Althausen and Thoenes: *ARCH. INT. MED.* **50**:46 [July] 1932) show similar decreases in blood sugar after the test in several animals, some of which were used later in the experiments with phosphorus.

If the experiment with chloroform will not bear criticism, it should not have been cited by Dr. Althausen as confirming his clinical results.

The instability of the sugar metabolism of rabbits only goes further to cast doubt on the application to man of results so obtained.

5. The previous reference to Migneco's article was incorrect. The figures given referred to the abstract which appeared in *The Journal of the American Medical Association*. The original article will be found in *Policlinico* (**40**:845 [May 29] 1933).

\* Koch, F. C.: Personal communication to the author. Laked blood was dialyzed until free from reducing substances when tested by the Folin copper method. Known amounts of glutathione were added to such laked blood and the reducing value in terms of dextrose determined by the Folin copper method on the tungstate blood filtrates.

HENRY T. RICKETTS, M.D., Chicago.

## Book Reviews

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**Clinical Science, Incorporating Heart.** Edited by Thomas Lewis, M.D., F.R.S. Volume 1. Number 1. Pp. 258. London: Shaw & Sons, Ltd., 1933.

In the letter which accompanies the first number of *Clinical Science*, Messrs. Shaw and Sons remind one that the journal *Heart* was started just twenty-four years ago. "At that time cardiac problems were being studied with unusual intensity, and a journal specially designed to publish original work dealing with the physiology and pathology of the cardio-vascular system had become a necessity to workers in that field. *Heart* successfully fulfilled that purpose. Even at its conception it was realized that in the course of time the flow of original work would diminish and the rate of publications decline. It is now felt that the time has arrived to widen its scope in order to maintain its standards of publication." Whether or not one agrees with the attitude of Messrs. Shaw, the idea of restricting the field of highly specialized medical journalism stimulates reflections. To begin with, every worker in medicine must agree that the number of publications has assumed such magnitude as in itself to constitute a serious problem. To read all the journals, or even to skim them, is physically impossible, and one looks forward to their arrival not with pleasure but with despair. If this colossal mass of material represented in large part new and valuable additions to knowledge, or even the results of genuine endeavor, one would be forced to be patient, if not pleased; unfortunately much of what is printed adds nothing either to ideas or to knowledge, and considerable is beneath criticism or even contempt. The causes of this state of affairs are not far to seek if one analyzes the contents of current journals. The most vicious type of paper is that which is produced merely for the purpose of bringing the author into print. Why editors admit to their pages essays obviously compounded from standard textbooks or reports of cases in which nothing new is brought out remains a mystery. Another type of article, especially prevalent at present, is that which "gilds the lily." Here material which is familiar to all is restudied, and the results are expressed in mathematical terms. The principle is a sound one since the quantitative evaluation of biologic data is of undoubted value, but the opportunities for exploitation are enormous. Finally there are those contributions which are, to be sure, original but in which no rational question is asked or useful answer produced; the reviewer recalls the incident of the weary professor who said to the student plaguing him for a topic for research, "Get some blood from mice and analyze it for arsenic; that's never been done before."

Another problem which confronts harassed editors is that of the manner rather than the matter of the manuscript. Infelicity of style and even bad grammar may be passed over, but the common practice of extending to twenty or more printed pages what could be adequately said in five or six is inexcusable. "The greatest possible number of words is used to express the smallest quantity of ideas," and the essence of the thesis after being anticipated in the introduction is labored in the body of the paper, recapitulated in tables, resummarized in the discussion and finally exposed yet again in the conclusions. Space is often wasted with bibliographies which are long but serve no real purpose, since they are not definitive, and with undue detail as to method. As a rule original work can be adequately presented in from five to fifteen pages; if more space is necessary, the subject is usually multiple and should be divided into several communications.

In the ardor of stating the case against certain vices of medical journalism, the reviewer must hasten to say that none of the criticisms applies to the new journal. The entire contents of the number emanate from the medical unit or

from the department of clinical research of University College Hospital. A variety of topics is dealt with: the physiologic action of insulin, pain derived from the skin, the action of digitalis, angina pectoris and renal function. Space forbids a discussion of the individual articles; suffice it to say that they all deal with the results of original work of a high order. The same careful editing notable in *Heart* under the leadership of Sir Thomas Lewis is evident in *Clinical Science*, which has retained the old format. It is to be hoped that Sir Thomas' name will continue to appear as frequently as in the past among the list of contributors; at any rate, one may be assured that a high standard of excellence will be maintained.

**L'hypoglycémie.** By Jean Sigwald. Price, 45 francs. Pp. 320. Paris: Gaston Doin & Cie, 1932.

The growing interest in hypoglycemia is manifested by this comprehensive monograph which contains information drawn from more than five hundred sources. Since the commonest experience with hypoglycemia has followed insulin therapy, most of the publications have appeared since 1922. The condition was noted, however, under certain circumstances long before. It is recalled that nervous symptoms accompanying depression of the blood sugar which occurred after the administration of phlorhizin were described by Fischler in 1913 as "intoxicatio glykopriya." This term, or "glycopenic complex," now suggested by Sigwald, seems to be appropriate in describing the hypoglycemic syndrome; the latter term fixes attention on the change in the blood, yet the symptoms of deficiency of dextrose do not always parallel the changes in blood sugar.

The clinical signs and symptoms are discussed exhaustively, and special attention is given to the various nervous manifestations. It is pointed out that the picture may be identical although the syndrome may arise from distinctly different causes. The etiologic factors include: (a) hypoglycemia due to a deficiency of carbohydrate in the organism, resulting from deficient intake (extreme undernutrition or starvation), abnormal elimination (renal glycosuria, lactation) or decline in carbohydrate storage due to overexertion, damage to the liver or defects of the muscular system; (b) hypoglycemia due to endocrine disorders, affecting the pancreas, suprarenal glands and pituitary gland; (c) hypoglycemia due to nervous disorders.

Hyperinsulinism due to islet tumor of the pancreas is presented by lengthy quotation from the original report of Wilder, Allan, Power and Robertson. Other cases which have been reported by American and Canadian authors are described, and attention is directed to the success of surgical extirpation of a pancreatic tumor in relieving severe hypoglycemic symptoms, first accomplished by Howland, Campbell, Maltby and Robinson.

The clinical observations of Harris, which first suggested in 1924 the possibility of overfunction of the pancreas, are discussed, and personal observations are given by the author on a case with intense spontaneous hypoglycemia in which hyperinsulinism was suspected. Yet, in these cases in which a lesion of the pancreas has not been demonstrated by surgical operation or autopsy it is impossible to make the diagnosis of hyperinsulinism with certainty.

The book shows successfully the need for clinical recognition of hypoglycemia by thorough acquaintance with its diverse manifestations, and shows further the various factors which must be considered in determining its origin when it occurs spontaneously.

**Studies from the Institute for Medical Research, Federated Malay States, Number 21. Melioidosis.** By A. T. Stanton, C.M.G., M.D., F.R.C.P., and William Fletcher, M.D., M.R.C.P. Cloth. Pp. 59, with 37 illustrations. London: John Bale Sons & Danielsson, Ltd., 1932.

This book is composed of material which, for the most part, has appeared under the name of the authors at various times between 1917 and 1927. The causative organism was first described by Whitmore in 1913 and named *Bacillus*

*pseudomallei*, on account of its similarity to the organism of glanders and because the disease caused by this organism in human beings resembled human glanders. Eighty-three cases have been reported, most of which have occurred in Burma and Malaya. Only two patients have survived. The symptoms of the disease and the pathologic changes are indistinguishable from those in glanders. The organism differs from *Bacillus mallei* in that it is motile and usually forms a wrinkled growth on glycerin agar. The authors have described an epidemic among laboratory animals (rabbits, guinea-pigs and rats) in Kuala Lumpur probably caused by food that had been contaminated by wild rodents, which are presumably the reservoir of the infecting organism. They suggested the name *Bacillus whitmori* for the organism in 1921, and later (1925) pointed out that *B. whitmori* and certain strains of *B. mallei* were serologically alike.

There is no evidence of direct infection from one human being to another. Apparently infection may occur in wounds or through the gastro-intestinal tract. In fully developed cases the organisms may be cultured from the blood. The authors believe that infection is usually due to food which has been contaminated by infected rodents.

A diagnosis of melioidosis can be made only by the isolation and identification of the organism. Death usually occurs before agglutinins appear in the blood.

The illustrations show the similarity of the lesions to the lesions of glanders. Caseous nodules in the lungs, liver and spleen are common. They may occur in almost any part of the body.

*B. whitmori* may be differentiated from *B. mallei* as follows: *B. whitmori* is motile, *B. mallei* is not; *B. whitmori* usually gives a wrinkled growth on glycerin agar, *B. mallei* gives a smooth growth; *B. whitmori* liquefies gelatin rapidly, *B. mallei* either fails to liquefy gelatin or does so very slowly.

The authors believe that many more cases of melioidosis occur than are recognized, owing to the fact that there are inadequate laboratory facilities available for diagnosis.

**A New Approach to Dietetic Therapy (Metabolism of Water and Minerals and Its Disturbances).** By Eugene Foldes, M.D., Formerly Assistant Professor of Medicine, University of Budapest, Hungary. Cloth. Price, \$5. Pp. 434. Boston: The Gorham Press, 1933.

The author of this most unusual volume attempts to show that such conditions as epilepsy, eclampsia, migraine, angina pectoris, bronchial asthma, allergic diseases, gout, essential hypertension, pernicious anemia, polycythemia, acne vulgaris, nervous and psychic disturbances, constitutional changes and aging have a common etiologic basis, namely, a disturbance in water and mineral metabolism. This disturbance may be either a generalized retention of water and salts or, as in migraine, angina pectoris and bronchial asthma, a local mobilization of fluids in the organs chiefly affected. The susceptibility of the person to such disturbances and the particular disease manifestation which results in any given case are supposed to depend on the "constitution" of the patient. The author enumerates and describes four such constitutional classes.

For all the aforementioned clinical conditions, the author advises "anti-retentional" treatment. This, as the name indicates, is designed to cause the organism to excrete its excess of water and salt. The treatment is largely dietary and consists essentially of a high protein, moderate carbohydrate, low fat diet. Water, salt and calories are moderately restricted. The use of diuretics is deprecated, but phenobarbital is recommended in those conditions in which local mobilizations are supposed to occur. Case reports are included to show the effectiveness of such treatment.

Although much of the material in this book is frankly speculative and many of the analogies drawn in support of the author's views are rather far-fetched, his hypothetical structure hangs together remarkably well. To those who have not been

exposed to the opinions contained therein, this volume offers at least some stimulating mental exercise. The very violence with which the author's ideas will be opposed by many of his readers, by initiating new thought and work, may constitute a large portion of whatever merit this book may have.

**Chronic Arthritis and Fibrositis. Diagnosis and Treatment.** By Bernard Langdon Wyatt, M.D. Price, \$3.50. Pp. 201. New York: William Wood & Company, 1933.

This book presents in a concise manner much of the valuable information that has resulted from recent investigations in the field of arthritis. It opens with a statistical and economic statement in regard to the prevalence and importance of chronic arthritis. The second chapter presents various considerations in regard to the etiology and pathology of chronic arthritic disease. Of especial note is the effort made to evaluate the various influences of focal infection, trauma and metabolic disturbances. With a view to its bearing on subsequent therapy, the author presents detailed considerations as to differential diagnosis and renders aid in giving laboratory technic for special examinations he regards as being of value.

Approximately half of the book is devoted to therapy. The author's recommendations for diet are clear and show a desirable caution about undue enthusiasm for this method of therapy. The accepted methods of physical therapy are described and discussed in such a manner as to guide the general practitioner quite satisfactorily. The various drugs are discussed similarly. The view that chronic arthritis is a local expression of constitutional disease is clearly indicated, and the measures directed toward its alleviation should support the organism as a whole.

The book is only in part a presentation of the author's experience. It constitutes a valuable summary of chronic arthritis and will be a useful guide to practitioners of general medicine and to those specializing in this field.

**Traité de physiologie normale et pathologique. Tome IX. Systeme nerveux (première partie).** By Roger and Binet. Price, 100 francs. Pp. 556. Paris: Masson & Cie, 1933.

This volume is part of the large system of normal and pathologic physiology by Roger and Binet designed along lines similar to those of the German work of Bethe and Bergmann. Attempts of this sort to bridge the gap between pure science and the clinic are altogether commendable, and the only criticism to be made is that the very size of the compendium precludes extensive use by the practicing physician, the man who could profit especially by it. In brief, there is danger of the compendium becoming a mausoleum.

The present volume is thoroughly done by competent men such as Binet, Cornil, Gley, Lhermitte, Nicloux, Richet and others. The initial topics are purely physiologic, such as an anatomic and physiologic description of the neuron. Matters bordering on pathology—degeneration, reflexes and tropisms—are dealt with next, followed by clinical and physiologic chapters on sensation, motility and neurologic localization. Finally come sections largely of clinical interest, such as convulsions and anesthesia. The writing is good, and one gets the impression of an adequate summary of current knowledge. Here and there is some overlapping, and unevenness can never be altogether avoided in a composite work of this sort.

**Pour combattre les troubles digestifs.** By Leon Schekter. Price, 15 francs. Pp. 119. Paris: Gaston Doin & Cie, 1932.

This small book is essentially a primer written for the layman. It contains a short table giving the protein, carbohydrate and fat content of common articles of diet and the components of a balanced diet. A short section is devoted to beverages and the effect of alcohol on the gastro-intestinal tract.

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